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Following Adjuvant Chemotherapy for Breast Cancer: Pilot
Study to Evaluate Incidence

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13. ABSTRACT (Maximum 200 Words) A serious late complication associated with breast cancer treatment is the increased risk for development of therapy-related hematologic malignancies. The goal of this biologic study is to determine whether dose-intensive adjuvant regimens for breast cancer induce genetic damage to hematopoietic stem cells, defined by the emergence of clonal hematopoiesis. Clonal hematopoiesis has been proposed as an early marker of hematopoietic stem cell damage, preceding the acquisition of critical, recurring genetic alterations associated with the development of therapy-related myelodysplastic syndromes and acute leukemia. Clonal hematopoiesis is being evaluated by two different methods, the X-linked HUMARA clonality and microsatellite instability assays. Positive clones will be further analyzed for <i>MLL</i> and <i>RAS</i> alterations. Study accomplishments to date: a) Clonal hematopoiesis biological protocols (S9719 and S0012) written and approved for study by DOD, CTEP and CTSU; b) clonality assays developed and standardized; c) S9719 biologic study incorporated into S0012, new clinical treatment protocol on 12/15/2001, due to the early closure of the companion clinical protocol, S9623; d) as of October 15, 2004 504 samples have been submitted for study, including 29 patients registered to S9719 (completed) and 168 patients registered to S0012; e) to increase assay sensitivity, the manual HUMARA method was modified to the ABI-3100 automated platform and a similar revision is in progress for the MSI assay; and f) the amendment to add paclitaxel, and eliminate estrogen receptor status and offer clonal hematopoiesis testing was made mandatory in 2003, substantially increasing patient accrual.			
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INTRODUCTION

The goal of this study is to determine whether dose-intensive adjuvant regimens for breast cancer induce genetic damage to hematopoietic stem cells, defined by the emergence of clonal hematopoiesis. Originally, the study was designed to study sequential blood/bone marrow samples from 200 women enrolled in a single, randomized dose-intensive Southwest Oncology Group (SWOG) adjuvant breast cancer study for women with four or more positive nodes (S9623, "A Comparison of Intensive Sequential Chemotherapy using Doxorubicin plus Paclitaxel plus Cyclophosphamide with High Dose Chemotherapy and Autologous Hematopoietic Progenitor Cell Support for Primary Breast Cancer in Women with 4 or More Involved Axillary Lymph Nodes, Phase III, Intergroup").

Due to poor accrual, S9719 was closed at the time the clinical treatment protocol (S9623) was closed. In December 2001, the clonal hematopoiesis project (S9719) was incorporated into S0012, a randomized comparison of standard doxorubicin and cyclophosphamide vs. weekly doxorubicin and daily oral cyclophosphamide plus G-CSF as neoadjuvant therapy for inflammatory and ER negative locally advanced breast cancer. However, to increase accrual for this protocol, the Southwest Oncology Group Breast Cancer Committee felt a revision was critical. A draft revision to add paclitaxel to both treatment arms and to drop the estrogen receptor negative requirement was submitted to CTEP on May 22, 2002. Additionally, we were required to submit the revision to the Central IRB (CIRB) for approval before CTEP would issue theirs. (This is due to CTSU participation on all Phase III studies.) CIRB requested additional changes and resubmission was submitted to CIRB by July 26, 2002 for their review on August 19, 2002. Accordingly S0012 was renamed "S0012, A Comparative Randomized Study of Standard Doxorubicin and Cyclophosphamide Followed by Weekly Paclitaxel Vs. Weekly Doxorubicin and Daily Oral Cyclophosphamide Plus G-CSF Followed by Weekly Paclitaxel as Neoadjuvant Therapy for Inflammatory and Locally Advanced Breast Cancer".

To encourage patient enrollment, the design of this study is simple. Four peripheral blood samples are collected from each patient over the course of their treatment, at 12 to 18 months. Two different general assays are used to detect clonality: the HUMARA (human androgen receptor) assay to estimate the incidence of early genetic damage defined by the presence of clonal hematopoiesis, and microsatellite instability testing to screen for loss of heterozygosity or the presence of defective DNA mismatch repair mechanisms. In cases where the HUMARA and microsatellite repeat assays are positive for clonality in two consecutive samples, the incidence of *MLL* fusion gene transcripts and *RAS* gene mutations (*H-*, *K-*, and *N-RAS*) will be examined.

BODY OF PROGRESS REPORT

Problems encountered in accomplishing study objectives as described in the original Statement of Work and proposed solutions:

In year 1, the clonal hematopoiesis protocol (S9719) was activated as a companion protocol to S9623 on schedule (October 15, 1997). Despite the advertisements and protocol presentations, patient accrual was slower than anticipated. A 1998 survey indicated two barriers: 1) short staffing of research nurses/clinical research associates at member institutions required the necessity to delete non-treatment directed trials and 2) the requirement of two separate consent forms was perceived as cumbersome for medical professionals and their patients. These concerns were ameliorated by drafting and submitting protocol amendments to the Department of Defense (DOD) and Cancer Therapy and Evaluation Program (CTEP) to incorporate S9719 directly into the primary treatment protocol (S9623). Draft amendments for S9623/S9719 were submitted to the Department of Defense Human Use Review Specialist on June 15, 1999 for DOD review and approval. The formal DOD and CTEP review process took ~13 months (official written approval was received July 11, 2000). The amendments were incorporated into S9623/S9719 and distributed to Southwest Oncology Group investigators in the Group mailings dated 7/15/00 and 9/15/00. Unfortunately, at the Fall 2000 meeting, the Southwest Oncology Group Data and Safety Monitoring Committee made the announcement that S9623, the companion clinical treatment trial, was targeted for closure due to poor accrual. One factor appeared to be that the highly emotional and controversial use of high dose chemotherapy and autologous stem cell transplantation (HDC-ABMT) for the treatment of breast cancer resulted in a significant decrease in patient accrual (if necessary, please refer to "Controversy Surrounding High Dose Chemotherapy" submitted as part of the 1999-2000 progress report). Please to continue the study were submitted to Dr. Charles A. Coltman. However, after considerable review, S9623 and S9719 (the companion DOD clonal hematopoiesis protocol) were closed on February 15, 2001.

As mentioned above, we received preliminary approval from the Acting Chair, HSRRB via Louise M. Pascal, RN, MS to proceed with our proposal to integrate the clonal hematopoiesis study into S0012, a randomized comparison of standard doxorubicin and cyclophosphamide versus weekly doxorubicin and daily oral cyclophosphamide plus G-CSF as neoadjuvant therapy for inflammatory and estrogen-receptor negative locally advanced breast cancer, phase III on August 20, 2001 culminating in protocol activation on December 15, 2001. However, accrual concerns rose again due to the lack of a taxane and the estrogen receptor negative requirement. A draft revision to add paclitaxel to both treatment arms and drop the estrogen receptor negative requirement was submitted to CTEP on May 22, 2002. Additionally, we were required to submit the revision to the Central IRB (CIRB) for approval before CTEP would issue theirs. (This is due to CTSU participation on all Phase III studies.) CIRB requested additional changes and resubmission was submitted to CIRB by July 26, 2002 for their review on August 19, 2002. Accordingly S0012 was renamed "S0012, A Comparative Randomized Study of Standard Doxorubicin and Cyclophosphamide Followed by Weekly Paclitaxel Vs. Weekly Doxorubicin and Daily Oral Cyclophosphamide Plus G-CSF Followed by Weekly Paclitaxel as Neoadjuvant Therapy for Inflammatory and Locally Advanced Breast Cancer".

Thus, the progress update for year 2003-2004 (year 6) describes the results to date for both S9719 and S0012. Funding to the third party institutions is based on accrual. So far we have paid out or are in the process of paying out 89.3% of funding against 94.1 % accrual. Additional funding will be disbursed to the testing centers as accrual continues.

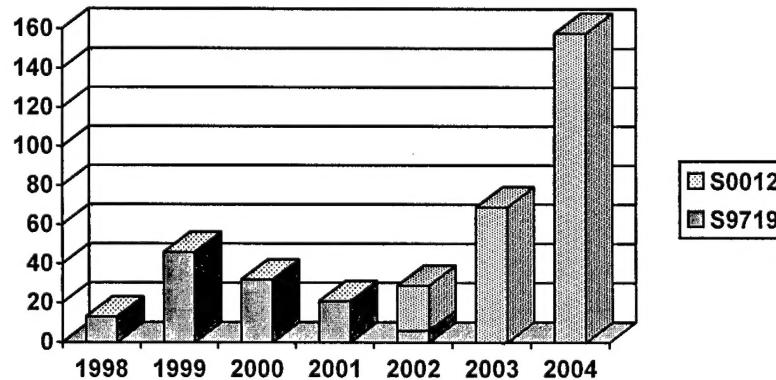
Experimental Design (S9719/S0012) Purpose: To test the hypothesis that genetic damage defined by the presence of clonal hematopoiesis can be detected in a subset of patients following dose-intensive adjuvant therapy.

Rationale for Clonal Hematopoiesis Project (S9719/S0012): Adjuvant therapy with anthracycline-based combination chemotherapy for patients with breast cancer improves disease-free and overall survival. Unfortunately, therapy-related myelodysplasia (t-MDS) or therapy-related acute myeloid leukemia (t-AML) have emerged as uncommon, but well-established, complications of adjuvant therapy using dose-intensive regimens for breast cancer. According to the Jacobs' model of leukemogenesis (1), t-MDS/t-AML evolves as a result of expansion of an abnormal clone of hematopoietic stem cells, which have acquired somatic mutations conferring a growth advantage. This damage may result in clonal proliferation, which, according to the Jacobs model of neoplasia, is an essential early (? initial) step in leukemogenesis, occurring prior to the development of clinical abnormalities.

Progress Update for 2003-2004:

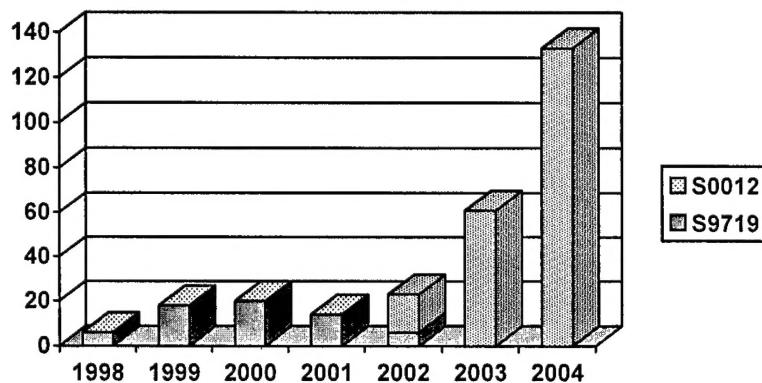
2003-2004 Patient Accrual. As of October 15, 2004, a total of 504 samples have been submitted for clonal hematopoiesis evaluation from 29 patients registered to S9719 and 168 patients registered on the newer clinical protocol, S0012. As seen in Figure 1, the number of patients registered to this companion biologic study has more than doubled in the past year, indicating the recent amendments to add paclitaxel and revise the estrogen receptor status are clearly resulting in increased patient accrual.

Figure 1. Clonal Hematopoiesis patient accrual since inception (S9719/S0012). The total number of samples received has more than doubled in the past year, clearly indicating the amendments to the protocol have resulted in increased accrual. S9719 samples, gray boxes and S0012, dotted boxes.



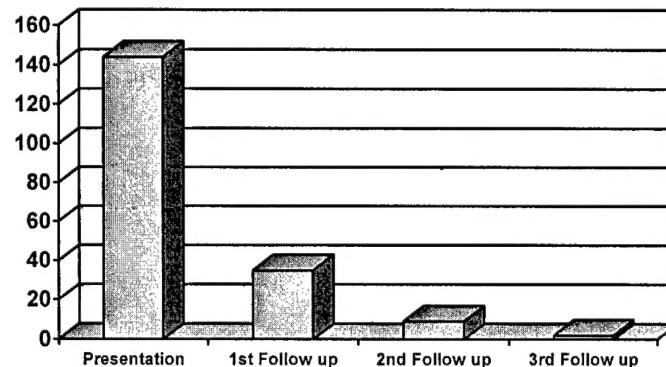
This point is further underscored in Figure 2, which shows the number of new patients registered to the clonal hematopoiesis study since the project started to receive samples in 1998. Figure 2 illustrates that the number of new patients registered in 2004 has more than doubled since 2003 and roughly equals the number of new patients registered over the past 6 years collectively. We are now confident that we will be able to complete the clonal hematopoiesis study as written in the Statement of Work using samples collected from S0012.

Figure 2. New patient registration by year for the DOD clonal hematopoiesis study. The number of new patients registered to study in 2004 was 133 compared to 61 patients in 2003, and 17 patients in 2002. The registration for S9719 was poor as explained in the introduction and problems encountered.



The last point that we would like to comment upon relates to follow-up samples. Figure 3 shows the number of presentation versus follow-up samples for patients registered to the clonal hematopoiesis study of S0012. Because year 2003-04 was the first year with the new amendments in place to increase patient accrual, our current data are lacking in follow-up time points to make any firm conclusions in our cohort. Thus, this progress report describes preliminary findings only. We have noticed that a few patients missed one scheduled time point, thus we are planning to contact to the attending physicians through the Southwest Oncology Group Statistical Center as a reminder to submit follow-up blood samples for this project. Such an approach was employed for S9719 and we received the required in follow-up samples in most cases with the exception of those patient who elected not to continue (Table 1). Please see section on "**Reasons for lack of follow-up samples**".

Figure 3. Sample submission by time point for S0012 patients who consented to participate in the DOD clonal hematopoiesis study. As indicated in Figure 2, patient registration was significantly increased in 2004. Follow-up sample collection at three additional time points occurs during their treatment course.



HUMARA Assay -- Dr. Marilyn L. Slovak

To date, we have accessioned 252 Southwest Oncology Group submissions (504 samples) from 197 patients. These submissions are from 168 patients registered on S0012 and 118 samples from 29 patients registered on S9719. The HUMARA and MSI data for all S9719 who agreed to participate in the study to completion are summarized in Table 1. All samples were within normal limits. Lacking positive findings, there was no reason to perform MLL RT-PCR testing and RAS mutation studies in this subset of patients; however, these assays will be performed for all positive patients.

One problematic situation surfaced during the processing of the S9719 samples. We noticed a low DNA yield in some follow-up samples, that is, during treatment. This situation required us to develop and validate a new more sensitive HUMARA assay than the standard gel electrophoresis method. Once we validated the assay and

instrumentation, we re-ran the residual S9719 sample material using the ABI 3100 automated capillary electrophoresis instead of manual acrylamide gel electrophoresis. Our data showed concordance between the two methodologies even though we were using smaller amounts of DNA. This new method has been incorporated resulting in increased sensitivity, productivity and sample throughput. We are currently developing a similar method for the MSI studies (see section below on MSI progress).

During the past year, we have processed 234 samples from patients on S0012. Of these, eight newly registered patients have shown either skewed X inactivation or positive clonal hematopoiesis in their pretreatment samples by the HUMARA assay (Figure 4). These eight samples have clonality ratios at or above 3, or greater than 75% of one allele, a finding considered positive for clonality (2,3). The Southwest Oncology Group numbers for these eight worrisome patients are: 183462, 183641, 181053, 184575, 183146, 185835, 188231, and 188389. Only two of these eight patients have follow-up samples where the alleles are remain "skewed" but the ratio is below 3. Thus, further evaluation is necessary to classify these patients as positive for clonal hematopoiesis or "excessive skewed" inactivation.

Skewed X inactivation may be the result of chance, or genetic factors involved in the X inactivation process or a selection process (4,5). When a particular sample is skewed, determination of clonal hematopoiesis becomes more difficult. Preferential PCR amplification and nested PCR due to low DNA yield exacerbate the problem. Because we have agreed to perform these analyses in a blind fashion without any knowledge of the patient's characteristics or treatment regimen, we recommend continued monitoring to rule true clonal hematopoiesis associated with a predisposition for secondary or therapy-related myelodysplasia, versus true skewed X-inactivation purported to be a risk factor in young breast cancer patients (6) and invasive ovarian cancer, especially in patients with a BRCA1 mutation (7). Serial samples of these patients are also needed to rule out possible chemotherapy effects since chemotherapy may cause neutropenia and lymphopenia (8), an age-related phenomenon that may mimic a skewed pattern (8-10), suboptimal DNA samples due to transit factors, or technical induced artifact such as nested PCR of the T-cell (control) fraction that may result in a false positive result. Thus, no conclusions can be drawn at this time.

Microsatellite Analysis – Dr. Wendy Stock

During the past year, material from 107-paired samples was shipped to our laboratory between 5/24/04-7/12/04 for analysis. However, after careful screening, only 48-paired samples were found to be evaluable based on DNA quality and quantity. Of these, 30 samples have been fully processed for PCR amplification of 5 microsatellite regions (BAT40, BAT26, APC, D2S123, and Mfd15). Due to concern about low PCR product yields with the first 30 samples, the remaining 18 samples have been stored until analysis of the first 30 samples is completed. MSI analysis on these 30 samples has not yet been completed since the ABI377 available to the Stock/Sher lab at the University of Chicago is not sufficiently sensitive for detecting low levels of DNA amplification. Therefore, plans are underway to complete the MSI analysis using a more sensitive machine located at the City of Hope National Medical Center.

Dr. Stock was originally funded to do the work at the University of Illinois and funding in the amount of \$37,046 was provided to institution. Funding to the institution was calculated based on accrual to the study. At different accrual increments, further funding would be provided to the institutions for continued support. In 2003, accrual had reached the next level of funding. The Southwest Oncology Group Operations Office then received notification that Dr. Stock had moved from the University of Illinois to the University of Chicago. The Group and the University of Chicago took time to negotiate a new subcontract, which was recently executed. Additional funds are forthcoming to the institution to support Dr. Stock and their work on this study.

Table 1. Update for 29 patient samples registered to S9719

Patient ID	Pretreatment HUMARA/MSI*	Apheresis HUMARA/MSI	3 Month HUMARA/MSI	~1 Year HUMARA/MSI	Addition Follow-up HUMARA/MSI
173752	1.95		1.35	1.8/- MSI	1.02/- MSI
174043	1.45		1.55	1.05/- MSI	
172865	1.4		No granulocytes	1.16/- MSI	
164513	1.33/ - MSI			1.20/ - MSI	1.20/ - MSI
169826	1.25/ - MSI			1.10/ - MSI	
172932**	1.48				
163674	1.23/ - MSI			1.25/ - MSI	1.10/ - MSI
169380	1.20/ - MSI	1.45/ - MSI	1.30/ - MSI	1.6/ No gran	
166131	1.55	1.15	No gran	**	
166282	1.65/ - MSI	1.10/ - MSI	No gran	1.25/ - MSI	
169229	1.18/ - MSI		1.25/ - MSI	1.05/ - MSI	
163093**	No gran/- MSI				
164598***	1.15/ - MSI				
169452	1.45/ - MSI		1.10/ - MSI	1.70/ - MSI	
167501	1.18/ - MSI		1.45/ - MSI	1.15/ - MSI	
169820	1.13/ - MSI			1.30/ - MSI	2.4/ NA
167233***	2.00/ - MSI				
174311	2.05/ NA	1.27/- MSI		1.38/- MSI	
173211	1.25/ - MSI		1.10/ - MSI	****	
172127	1.10/ NA	1.40 / NA		1.55 / NA	
164192	1.05/ - MSI		1.15/ - MSI	1.20/ - MSI	
165292	1.18/ - MSI	1.70	No gran	1.15/ - MSI	
168599	1.0/ - MSI			1.42/ - MSI	
168656	Monoallelic/- MSI		- MSI	- MSI	
168659	1.45/ - MSI	1.05/ - MSI	1.10/ - MSI	1.3/ - MSI	
172716	1.38/ - MSI	1.10/ - MSI		1.15/- MSI	
166407	1.08/ - MSI		1.20/ - MSI	1.20/ - MSI	
167145	1.13/ - MSI	1.25/ - MSI	1.1/ - MSI	1.20/ - MSI	
166218	1.15/ - MSI	1.10/ - MSI		**	

*HUMARA results are expressed as a ratio (2). Random inactivation will show both maternal and paternal allele, signifying a polyclonal state; the presence of only one allele or shift of greater than 3-fold (to control for skewed X-inactivation over the other allele), will identify a clonal population (see reference 2 and previous progress reports). MSI is reported as positive (+) or negative (-).

**No follow up sample(s) available for this patient

***Patient went off study

****Off protocol due to progressive disease

No gran: the granulocyte layer was not of sufficient quantity to yield results.

Monoallelic: HUMARA assay is non-informative because the alleles cannot be distinguished.

NA: not analyzed

Figure 4

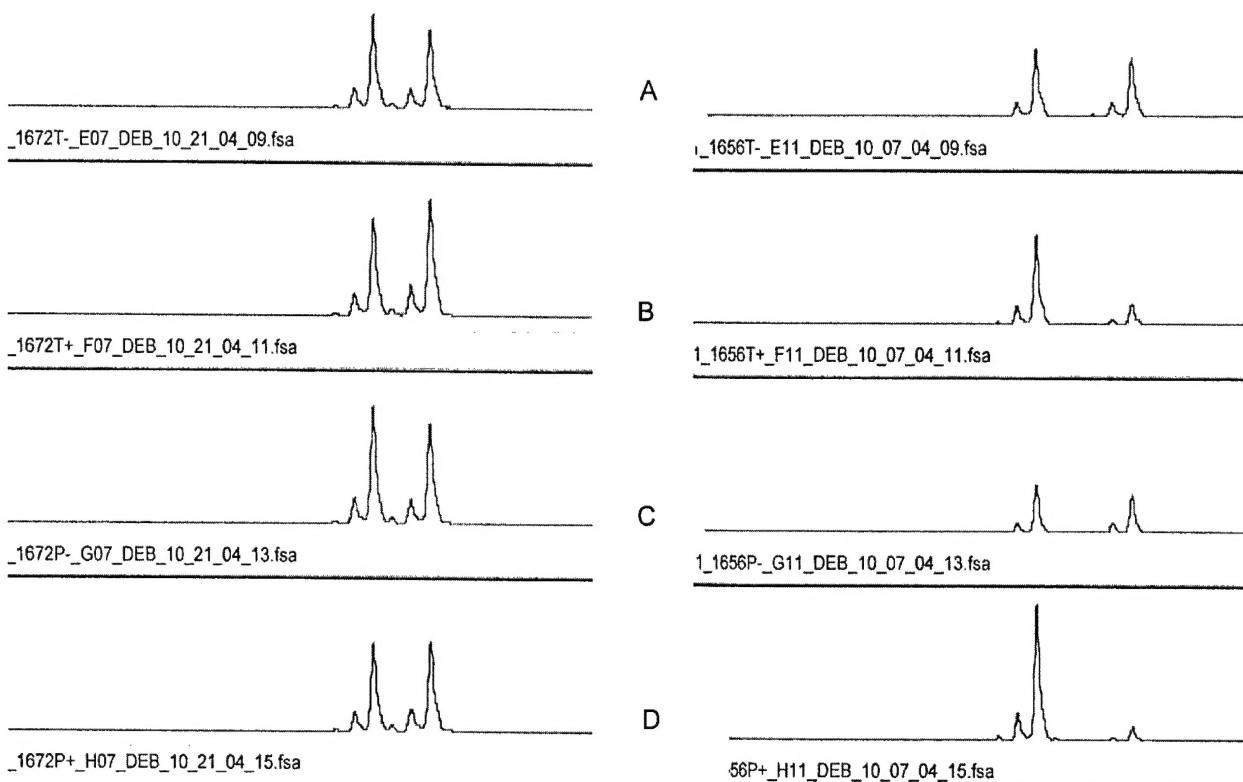


Figure 4. Line A for both electropherograms demonstrates T-cell DNA digested with the Rsa I enzyme, which is not sensitive to methylation status. Both alleles should be digested at the same rate therefore two relatively equal peaks will be observed. Line B represents T-cell DNA digested with the methylation sensitive Hpa II enzyme. Methylated DNA will not be cut. Unmethylated DNA is cut and therefore not amplified. In a normal sample, the methylated to unmethylated ratio is 50:50 due to random X inactivation. In a subset of patients, skewed X-inactivation is observed where the methylation status is not random. Line C represents PMN DNA digested with Rsa I enzyme. Again, relatively equal peaks are observed because methylation status is not assessed. Line D represents PMN DNA digested with Hpa II enzyme. Skewed samples will show a predominant allele due to non-random x-inactivation. This pattern is similar to that which would be observed if clonal hematopoiesis was detected in a sample. This illustrates the importance of our internal control to establish the inactivation pattern of each individual patient. By using the T-cell data we can correct for skewed X-inactivation.

Reasons for lack of follow-up samples:

S9719 Study Subjects. Three patients requested to come off S9719 study for the following reasons: toxicity (n=1), extreme difficulty in collecting blood (n=1), or a patient became uncomfortable with proposed stem cell collection procedure (n=1). Another patient was monoallelic and therefore non-informative by clonal hematopoiesis testing by the HUMARA assay. We distributed reminder letters for "past due" follow-up samples to the attending Southwest Oncology Group physicians on 9/5/2001. These letters resulted in the collection of the one-year blood collection time point for all but two patients registered to S9719.

S0012 Study Subjects. As of November 5, 2004, there are 257 patients registered to S0012 since 12/15/2001 when the clonal hematopoiesis study was added to the clinical protocol. Of the 246 not deemed ineligible, 27 have stopped treatment early for the following reasons:

7 patients due to progression: 181366, 181810, 181845, 183193, 183234, 186311, and 187604.

11 patients due to toxicity: 181470, 182964, 183101, 183230, 183366, 183670, 183675, 183715, 183957, 185330, and 186611.

9 patients for other reasons:

179062 (after 4 cycles, doctor thought there was not sufficient response to consider mastectomy)

181203 (patient wanted surgery prior to Taxol)

181199 (physician removed patient from study for "not much decrease in disease measurement")

182776 (patient could not afford Cytoxan)

184160 (congestive heart failure after one course)

184500 (refused treatment)

185261 (off study due to "personal beliefs")

185428 (withdrew consent)

186578 (patient was a no show and not returning calls after 5 week treatment delay)

A separate consent form is required for the clonal hematopoiesis study. Based on the above data, the number of patients registered to the clonal hematopoiesis study is approximately 70% of the patient's registered to the clinical protocol. As indicated in the reasons listed above, no S0012 patient went off study based on the clonal hematopoiesis study or its peripheral blood requirements. We plan to distribute reminder letters for "past due" follow-up samples to the attending Southwest Oncology Group physicians within the next three months.

Statistical considerations for clonal hematopoiesis study:

As of 10/29/04, the clinical study had 259 patients out of an accrual goal of 300 - with closure planned for some time in December 2004 or early January 2005. Based on current accrual estimates and goals, we are confident that we will be complete this study with the S0012 study population. Compliance with the blood drawn at the time of surgery should be nearly complete by January of 2006 at 12 months following completion of treatment. Approximately 15% of the patients might be anticipated to have relapsed or refused to participate and not have samples available. The probability of clonal hematopoiesis at a particular time point can be established to within ± 0.1 with a sample size of 100 per arm, and to within ± 0.1 with a sample size of 85. Change in status between pretreatment, at the time of surgery, and at six and twelve months post-surgery samples will be explored, as will concordance of the HUMARA and MSI assays. Association of treatment, pre-study patient characteristics, and tumor-related variables with presence or absence of clonality by HUMARA or MSI assays will also be explored.

The study is being monitored by the Southwest Oncology Group Data and Safety Monitoring Committee according to NCI guidelines and Southwest Oncology Group policy.

KEY RESEARCH ACCOMPLISHMENTS

- As of October 2004, a total of 252 Southwest Oncology Group submissions (504 samples) from 197 patients have been evaluated, including 29 patients registered to S9719 and 168 patients registered to S0012.
- Preliminary results show eight patients with an X inactivation pattern in their pretreatment sample

- consistent with either clonal hematopoiesis or skewed X inactivation by the HUMARA assay.
- No evidence of microsatellite instability (MSI) prior to the initiation of therapy or at time of follow-up detected, however: a modified, more sensitive MSI assay is being developed to test those samples with a smaller DNA yield.
- The HUMARA and microsatellite instability assays give reproducible and complementary results using sequentially obtained blood samples of women treated on this study.
- To increase assay sensitivity, the manual HUMARA method has been modified to the ABI-3100 automated platform.
- Peripheral blood T-lymphocytes are a useful internal, tissue-specific control for the HUMARA assay precluding the need for age-matched controls for skewed X-inactivation.
- On December 15, 2001, the clonal hematopoiesis study was incorporated and activated into a new Southwest Oncology Group breast cancer treatment protocol (S0012).
- Patient accrual to S0012 was substantially increased by an amendment to include a taxane and drop the estrogen receptor negative requirement. Accrual has more than doubled in one year.
- Study accrual will be met at completion of the S0012 clinical trial.

REPORTABLE OUTCOMES

Analysis of additional patients with longer follow-up is essential to confirm these preliminary results; however, at this point, neither regimen used in this setting (dose-intensive therapy with growth factor support vs. high-dose therapy with stem cell reinfusion for stage II/III breast cancer as described in S9623) appears to initiate genetic damage that could result in development of hematologic malignancies. S0012, activated on 12/15/01 and amended in 2003, has resulted in a substantial increase in patient accrual for the past year. Due to short follow-up, no publications are possible at this time.

CONCLUSIONS/FUTURE DIRECTIONS

This pilot study was designed to test the hypothesis that genetic damage, defined by the presence of clonal hematopoiesis, can be detected in a subset of patients following dose-intensive adjuvant therapy on a current Southwest Oncology Group trial for breast cancer. The salient points outlined in the grant application's "Statement of Work" have been addressed. During the first three years, the highly emotional controversy surrounding high dose chemotherapy with stem cell rescue for breast cancer has made a substantial deleterious impact on patient accrual to both the clonal hematopoiesis biological study and the clinical treatment protocol (S9623). Accordingly, to answer the important question of this study, we have incorporated this biological investigation into a less controversial but pertinent breast cancer treatment protocol. Low accrual was the major set back in this study; however, the amendments to S0012 in 2003 have corrected this situation. We firmly believe that we can complete this investigation within the same time frame as the companion S0012 clinical trial. The protocol is simple and consists of four blood drawings at four defined time points for those patients agreeing to participate in the study. Based on the first 250 patients who have registered to S0012 and have elected to go off study, none of them have indicated that participation in clonal hematopoiesis study was unacceptable to them. The biological questions of why this late effect complication only occurs in a subset of breast cancer patients, what the synergistic effects of other drugs or radiotherapy are, whether the period/sequence of drug administration matters, are patients predisposed, and are faulty DNA repair mechanism at play, remain problematic in the treatment of breast cancer. Furthermore, the supposition that an increase in skewing of X activation in females with breast or ovarian cancer may therefore be an indication of an effect of X-linked genes (6-7) warrant continuation of this project. Therefore, this DOD funded project remains unanswered and very relevant for breast cancer patients.

Confirmation that adjuvant chemotherapy induces clonal hematopoiesis in a significant number of patients from this pilot study will provide a unique model to prospectively study the evolution of therapy-related leukemogenesis in patients being treated for breast cancer, and would be the focus of a subsequent grant proposal. The goals of a larger study would include the following: 1) to determine whether a relationship exists between detection of clonal hematopoiesis and subsequent evolution to t-MDS/AML; 2) to identify general mechanisms (e.g., faulty DNA repair and mutations in components of cell cycle checkpoints), which may predispose patients to genetic instability and leukemogenesis, following adjuvant therapy; 3) to determine the sequence of events (genomic instability, loss of heterozygosity, specific mutations/ translocations, etc.) which participate in leukemogenesis; and 4) to determine whether specific adjuvant regimens place patients at an unacceptably high risk for the

development of therapy-related hematologic malignancies. If the study is negative, two conclusions are possible: (1) high risk breast cancer patients can rest assured that they can receive high dose chemotherapy, without an increased risk of development of clonal hematopoiesis or subsequent evolution to a therapy-related hematopoietic disorder over the general population or (2) clonal hematopoiesis is not the route to leukemogenesis. Additionally, this study may potentially shed light as to whether skewed X inactivation, or a factor associated with it, may be a risk factor for the development of breast cancer in a subset patients who may or may not have BRCA1 mutations (6,7).

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Appendix:

**S0012, “A Comparative Randomized Study
of Standard Doxorubicin and
Cyclophosphamide vs. Weekly Doxorubicin
and Daily Oral Cyclophosphamide Plus G-
CSF as Neoadjuvant Therapy for
Inflammatory and Estrogen-Receptor
Negative Locally Advanced Breast Cancer”**



**Southwest
Oncology Group**
A National Clinical Research Group

Distributed: June 15, 2004
Submitted to CTEP: May 14, 2004

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CTSU

FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0012**, "A Comparative Randomized Study of Standard Doxorubicin And Cyclophosphamide Followed by Weekly Paclitaxel Vs. Weekly Doxorubicin And Daily Oral Cyclophosphamide Plus G-CSF Followed by Weekly Paclitaxel As Neoadjuvant Therapy For Inflammatory And Locally Advanced Breast Cancer". Study Coordinators: Drs. G. Ellis, R. Livingston, M. Slovak, Ph.D., and Drs. W. Stock and K. Albain.

REVISION #5

Southwest Oncology Group Study Coordinator: Georgiana K. Ellis, M.D.
Phone: 206/288-2048
E-mail: gellis@u.washington.edu

IRB Review Requirements

- () Full board review required. Reason:
() Initial activation
() Increased risk to patient
() Complete study redesign
() Addition of tissue banking requirements
() Study closure not built into study design
- () Expedited review allowed
- () No review required

REVISION #5

The study reference above has been revised as follows:

1. The cover memorandum outlining "Amendment #3" has been revised to require full board IRB review of this protocol for NCCTG institutions planning to participate in the study, but no review is required for this amendment for institutions already participating in the study.
2. Page 1: NCCTG has been removed as a separate entry on the participant list as they have endorsed this trial via CTSU.
3. Page 1: The top corner of the title page has been revised to state "Amended 04/22/04" instead of "Revised 05/01/04", and a new "Revised 05/14/04" has been added.
4. Page 1: The version date has been updated.

Operations Office

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Please attach this memorandum to the front of your copy of the protocol and insert the replacement page.

This memorandum serves to inform the Southwest Oncology Group Statistical Center and the NCI.

cc: PROTOCOL & INFORMATION OFFICE
William Barlow, Ph.D.
Danika Lew, M.A,
Caroline Jiang, M.S.
Diana Lowry
Jean Barce
Janis Gjervik - NCCTG
Stephanie Edwards
Gity Nasim - EMMES
Kendra Godfrey Barrow - CTSU
Debra Litwak - Amgen
Col. Julie Zadinsky - DOD
Karen Stotler - DOD



**Southwest
Oncology Group**
A National Clinical Research Group

Distributed: June 15, 2004
Revision Submitted to CTEP: May 14, 2004
Distributed: May 15, 2004
Submitted to CTEP: April 22, 2004

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; NCCTG; CTSU

FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0012**, "A Comparative Randomized Study of Standard Doxorubicin And Cyclophosphamide Followed by Weekly Paclitaxel Vs. Weekly Doxorubicin And Daily Oral Cyclophosphamide Plus G-CSF Followed by Weekly Paclitaxel As Neoadjuvant Therapy For Inflammatory And Locally Advanced Breast Cancer". Study Coordinators: Drs. G. Ellis, R. Livingston, M. Slovak, Ph.D., and Drs. W. Stock and K. Albain.

AMENDMENT #3

Southwest Oncology Group Study Coordinator: Georgiana K. Ellis, M.D.
Phone: 206/288-2048
E-mail: gellis@u.washington.edu

IRB Review Requirements

- () Full board review required. Reason:
() Initial activation (**For NCCTG institutions only if this has not yet been performed**)
() Increased risk to patient
() Complete study redesign
() Addition of tissue banking requirements
() Study closure not built into study design
- () Expedited review allowed
- () No review required (**For institutions already participating**)

AMENDMENT #3

The study referenced above has been revised as follows:

1. The following Cooperative Group has endorsed this trial:

North Central Cancer Treatment Group (NCCTG): Co-chair: Edith A. Perez, M.D. **All Cooperative Group members who are not aligned with the Southwest Oncology Group will enroll patients to this study and submit data via the Cancer Trials Support Unit (CTSU).**

2. Page 2: The NCCTG has been added to the participant list and the contact information for the NCCTG study coordinator, Edith A. Perez, M.D., has been included.

Please attach this memorandum to the front of your copy of the protocol and insert the replacement pages.

Operations Office

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This memorandum serves to inform the Southwest Oncology Group Statistical Center and the NCI.

cc: PROTOCOL & INFORMATION OFFICE
Stephanie Green, Ph.D.
Danika Lew, M.A.
Caroline Jiang, M.S.
Diana Lowry
Jean Barce
Janis Gjervik - NCCTG
Stephanie Edwards
Gity Nasim - EMMES
Kendra Godfrey Barrow - CTSU
Debra Litwak - Amgen
Col. Julie Zadinsky - DOD
Karen Stotler - DOD



Distributed: April 1, 2004
Effective: January 30, 2004

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CTSU

FROM: Gilbert R. Carrazales, M.S., Protocol Coordinator

RE: **S0012**, "A Comparative Randomized Study of Standard Doxorubicin And Cyclophosphamide Followed by Weekly Paclitaxel Vs. Weekly Doxorubicin And Daily Oral Cyclophosphamide Plus G-CSF Followed by Weekly Paclitaxel As Neoadjuvant Therapy For Inflammatory And Locally Advanced Breast Cancer". Study Coordinators: Drs. G. Ellis, R. Livingston, M. Slovak, Ph.D., and Drs. W. Stock and K. Albain.

REVISION #4

Southwest Oncology Group Study Coordinator: Georgiana K. Ellis, M.D.
Phone: 206/288-2048
E-mail: gellis@u.washington.edu

IRB Review Requirements

- () Full board review required. Reason:
() Initial activation (should your institution choose to participate)
() Increased risk to patient
() Complete study redesign
() Addition of tissue banking requirements
() Study closure not built into study design
- () Expedited review allowed
- (✓) No review required

REVISION #4

The above noted study had been revised to include an expanded treatment start time frame.

Specific changes are listed below:

1. Title Page: The version date has been updated.
2. The Southwest Oncology Group Statistical Center address has been updated (title page).
3. Section 13.1 (page 29) has been updated to specify that the treatment start time frame has been expanded from 1 (one) to 5 (five) working days.

Please attach this memorandum to the front of your copy of the protocol and insert the replacement pages.

This memorandum serves to inform the Southwest Oncology Group Statistical Center and the NCI.

cc: PROTOCOL & INFORMATION OFFICE
Stephanie Green, Ph.D.
Danika Lew, M.A.
Caroline Jiang, M.S.
Diana Lowry
Jean Barce

Stephanie Edwards
City Nasim - EMMES
Kendra Godfrey Barrow - CTSU
Debra Litwak - Amgen
Col. Julie Zadinsky - DOD
Karen Stotler - DOD

Operations Office

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**Southwest
Oncology Group**
A National Clinical Research Group

January 1, 2004

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CTSU

FROM: Deepa P. Sahrawat, M.P.H., Protocol Coordinator

RE: **S0012**, "A Comparative Randomized Study of Standard Doxorubicin And Cyclophosphamide Followed by Weekly Paclitaxel Vs. Weekly Doxorubicin And Daily Oral Cyclophosphamide Plus G-CSF Followed by Weekly Paclitaxel As Neoadjuvant Therapy For Inflammatory And Locally Advanced Breast Cancer". Study Coordinators: Drs. G. Ellis, R. Livingston, M. Slovak, Ph.D., and Drs. W. Stock and K. Albain.

REVISION #3

Southwest Oncology Group Study Coordinator: Georgiana K. Ellis, M.D.
Phone: 206/288-2048
E-mail: gellis@u.washington.edu

IRB Review Requirements

- () Full board review required. Reason:
() Initial activation (should your institution choose to participate)
() Increased risk to patient
() Complete study redesign
() Addition of tissue banking requirements
() Study closure not built into study design
- (✓) Expedited review allowed
- () No review required

REVISION #3

The above noted study had been revised as follows:

1. The "NOTE" in the third paragraph of Section 15.4 (page 32b) has been deleted.
2. The Model Informed Consent has been revised to change the "University of Illinois at Chicago" to the "University of Chicago" in the last paragraph on page 42.

Replacement pages are enclosed for the above-mentioned pages. Please attach this memorandum to the front of your copy of the protocol and insert the replacement pages.

This memorandum serves to inform the Southwest Oncology Group Statistical Center and the NCI

cc: PROTOCOL & INFORMATION OFFICE
Stephanie Green, Ph.D.
Danika Lew, M.A.
Caroline Jang, M.S.
Diana Lowry
Jean Barce

Stephanie Edwards
Gity Nasim - EMMES
Juanita Tejada - CTSU
Debra Litwak - Amgen
Col. Julie Zadinsky - DOD
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Southwest Oncology Group

A National Clinical Research Group

Distribution Date: August 1, 2003
CTEP Submission Date: July 11, 2003

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CTSU

FROM: Deepa P. Sahrawat, M.P.H., Protocol Coordinator

RE: **S0012**, "A Comparative Randomized Study of Standard Doxorubicin And Cyclophosphamide Followed by Weekly Paclitaxel Vs. Weekly Doxorubicin And Daily Oral Cyclophosphamide Plus G-CSF Followed by Weekly Paclitaxel As Neoadjuvant Therapy For Inflammatory And Locally Advanced Breast Cancer". Study Coordinators: Drs. G. Ellis, R. Livingston, M. Slovak, Ph.D., and Drs. W. Stock and K. Albain.

REVISION #2

Study Coordinator: Georgiana K. Ellis, M.D. Phone: 206/288-2048
Email: gellis@u.washington.edu

IRB Review Requirements

- () Full board review required. Reason:
() Initial activation (should your institution choose to participate)
() Increased risk to patient
() Complete study redesign
() Addition of tissue banking requirements
() Study closure not built into study design
- () Expedited review allowed
- () No review required

REVISION #2

The study referenced above has been revised as follows:

1. Section 5.1, page 17, the statement "Punch biopsy is allowed if invasive breast cancer is documented" has been added.
2. The statement "Please refer to Section 8.4 for paclitaxel dose modifications" has been added to Sections 8.2 (page 23) and 8.3 (page 25).
3. The Paclitaxel*** footnote in Section 7.2 (page 19) and the Paclitaxel**** footnote in Section 7.3 (page 20) have been corrected to state "...150 mg PO ranitidine or 50 mg IV ranitidine 30 - 60 minutes prior to paclitaxel infusion (or equivalent)."
4. Section 7.8 (page 21) has been changed to state, "All patients will be followed for five years or until death..."

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5. Section 8.3c (page 25) has been added to outline the conditions and procedures for dose reduction in G-CSF.
6. Estrogen-receptor status is no longer required, therefore it has been removed from the "laboratory" section of the study calendars. The accompanying " μ " footnote has also been deleted (Sections 9.1, page 26 and 9.2, page 27).
7. Due to the change described in #6, the Estrogen-Receptor status information has been modified in the S0012 Breast Cancer Prestudy Form. The form has been updated. The new form number is 34877 (Section 14.6a, page 32 and Section 18.2b, page 38).
8. The Expanded Participation Project (EPP) Instructions (Appendix 19.1) has been updated (pages 57 - 60, page 61 was deleted).
9. The length of time for follow-up of patients has been corrected in the Informed Consent, stating "After one year you will be followed by physical exam annually for four more years. The total length of time for follow-up is five years." (Informed Consent form, "What is Involved in This Study?", page 42a)

Replacement pages are enclosed for the title page and pages 17, 19, 20, 21, 23, 25, 26, 27, 32, 38, 42a, 57 - 60, and the S0012 Breast Cancer Prestudy Form (Form #34877).

This memorandum serves to inform the Southwest Oncology Group Statistical Center and the NCI.

cc: PROTOCOL & INFORMATION OFFICE
Stephanie Green, Ph.D.
Danika Lew, M.A.
Caroline Jiang, M.S.
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Juanita Tejada/CTSU
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Col. Julie Zadinsky - DOD
Karen Stotler - DOD



Southwest Oncology Group

A National Clinical Research Group

January 15, 2003

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CTSU

FROM: Deepa P. Sahrawat, M.P.H., Protocol Coordinator

RE: S0012, "A Comparative Randomized Study of Standard Doxorubicin And Cyclophosphamide Followed by Weekly Paclitaxel Vs. Weekly Doxorubicin And Daily Oral Cyclophosphamide Plus G-CSF Followed by Weekly Paclitaxel As Neoadjuvant Therapy For Inflammatory And Locally Advanced Breast Cancer". Study Coordinators: Drs. G. Ellis, R. Livingston, M. Slovack, Ph.D., and Drs. W. Stock and K. Albain.

MEMORANDUM

Study Coordinator: Georgiana K. Ellis, M.D. Phone: 206/288-2048
Email: gellis@u.washington.edu

IRB Review Requirements

- () Full board review required. Reason:

 - () Initial activation (should your institution choose to participate)
 - () Increased risk to patient
 - () Complete study redesign
 - () Addition of tissue banking requirements
 - () Study closure not built into study design

() Expedited review allowed

() No review required

MEMORANDUM

If a patient reconsented to the above-noted study (protocol version dated 10/1/02) between 1/1/03 and 1/15/03, please complete the Notice of Reconsent. If the patient reconsented prior to 1/1/03, also complete this form.

Enclosed with this memorandum is the S0012 Notice of Reconsent.

This memorandum serves to inform the Southwest Oncology Group Statistical Center and the NCI.

cc: PROTOCOL & INFORMATION OFFICE
Stephanie Green, Ph.D.
Danika Lew, M.A.
Caroline Jiang, M.S.
Diana Lowry
Karin Rantala
Jean Barce

Stephanie Edwards
Gity Nasim/EMMES
Juanita Tejada/CTSU
Debra Litwak/Amgen
Col. Julie Zadinsky - DOD
Karen Stotler - DOD

**SOUTHWEST ONCOLOGY GROUP
S0012 NOTICE OF RECONSENT**

Page 1 of 1

Instructions: If the patient was registered to S0012 between 1/1/2003 and 1/15/2003 and reconsents to the 10/1/2002 version (Amendment #2), please submit the following information. If the patient was registered prior to 1/1/2003 and has reconsented, also submit this form.

Date is MONTH, DAY, YEAR. Explain a blank date in the Comments section. Circle AMENDED items in red.

SWOG Patient ID

SWOG Study No. **S0012**

Registration Step **1**

Patient Initials _____ (L, F M)

Institution/Affiliate _____ Physician _____

Date of Reconsent: / /

Please send this form to:

Southwest Oncology Group Data Operations Center
Cancer Research and Biostatistics
ATTN: Stephanie Edwards
1730 Minor Ave, STE 1900
Seattle, WA 98101-1468

Comments:

1/15/2003

6420





**Southwest
Oncology Group**
A National Clinical Research Group

Distribution date: January 15, 2003
CTEP Submission Date: November 22, 2002

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CTSU

FROM: Deepa P. Sahrawat, M.P.H., Protocol Coordinator

RE: **S0012**, "A Comparative Randomized Study of Standard Doxorubicin And Cyclophosphamide Followed by Weekly Paclitaxel Vs. Weekly Doxorubicin And Daily Oral Cyclophosphamide Plus G-CSF Followed by Weekly Paclitaxel As Neoadjuvant Therapy For Inflammatory And Locally Advanced Breast Cancer". Study Coordinators: Drs. G. Ellis, R. Livingston, M. Slovak, Ph.D., and Drs. W. Stock and K. Albain.

REVISION #1

Study Coordinator: Georgiana K. Ellis, M.D. Phone: 206/288-2048
Email: gellis@u.washington.edu

IRB Review Requirements

- () Full board review required. Reason:
() Initial activation (should your institution choose to participate)
() Increased risk to patient
() Complete study redesign
() Addition of tissue banking requirements
() Study closure not built into study design
- (✓) Expedited review allowed
- () No review required

REVISION #1

The above-noted protocol has been as follows:

1. The design change outlined in Amendment #2 will become mandatory for patients registered beginning January 1, 2003. Please refer to Amendment #2 for detailed information on the design change. This switch over date does not result in further changes to the protocol. Investigators are not recommended to switch patients already enrolled, to the new study design as described in Amendment #2.
 2. Section 14.7 (page 32) - has been updated.
 3. In Section 14.9 "copies of" was added after "Submit...".
 4. The **S0012** Breast Cancer Pre-Study Form (Form #62170) has been updated.
-

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5. In Section 15.3 (pg. 32b), "patient name" has been changed to "patient initials".
 6. At the request of CTSU, logistical updates and changes have been made in the following sections:
 - Table of Contents (pg. 2): The CTSU mailing address has been updated.
 - Section 13.5 (pg. 30): A paragraph beginning "In addition, all enrolling investigators..." has been added after the first paragraph.
 - Section 13.5 (pg. 30): Under "CTSU Procedures for Patient Enrollment", the CTSU Enrollment Coversheet has been changed to CTSU Patient Enrollment Transmittal Form and the word "Eligibility Check" has been changed to "Eligibility Criteria".
 - Section 14.4 (pg. 31 - 32): "Operations" has been added to the first paragraph after "CTSU Data". The first bulleted paragraph has been changed to read "Patient entry forms and adverse...". A third bulleted paragraph has been added. The CTSU address has been updated. A bold statement, which reads "A CTSU Data Transmittal Form should accompany all forms and reports submitted to the CTSU" has been added under the address.
 - The CTSU Adverse Event Reporting Guidelines have been updated on page. 35.
 - Section 15.6 (pg. 32c): This section has been added for CTSU Investigators.
 - The Model Informed Consent (pg. 39): A note has been added for CTSU Investigators.
 7. In Section 13.3 (pg. 30) "Statistical Center has been changed to "Data Operations Center in Seattle" and in Section 14.3 (pg. 31), the address for the Data Operations Center has been updated.
 8. Section 7.2 (pg. 19), the spelling of paclitaxel has been corrected.
 9. Section 7.3 (pg. 20), the second paragraph has been changed from "One week after completing of the AC + G regimen, paclitaxel will be given weekly for 12 weeks." to "After the last dose of cyclophosphamide, paclitaxel will be given weekly for 12 weeks."
- In the table for cyclophosphamide, "weeks" has been moved to the interval column underneath "continuous for 15".
- Paclitaxel interval has been changed to say "weekly x 12 weeks beginning after the last dose of cyclophosphamide.
10. Section 9.1 (pg. 26), Arm 1 calendar, a footnote has been added for paclitaxel stating, "Paclitaxel will be given weekly for 12 weeks beginning 3 weeks after completion of the last dose of AC."

11. Section 9.2 (pg. 27), Arm 2 calendar, a footnote has been added for paclitaxel stating, "Paclitaxel will be given weekly for 12 weeks beginning after the last dose of cyclophosphamide."

The "∞" footnote has been corrected to reference Section 7.3.
12. In the Model Consent Form (pg. 41), in the paragraph titled "If you're assigned to Arm 1", the second sentence has been changed from "One week..." to "Three weeks...".

In the paragraph titled "If you are assigned to Arm 2," the next to the last sentence has been changed from "One week after you finish this..." to "After you finish taking cyclophosphamide, you will receive...".
13. Section 5.18 (pg. 18) has been added stating, "Patients must not be planning to receive any concurrent anticancer therapy while receiving protocol treatment."
14. Section 5.19 (pg. 18) has been added stating, "For patient registered after January 1, 2003, the patient must have signed the revised consent form reflecting the study design changes distributed in Protocol Amendment #2. Not applicable if before 1/1/2003.
15. The **S0012** Registration Form (Form #13262) has been updated.
16. A page break error has been corrected on pages 8a and 8b.
17. Page 56a has been renumbered to 56.

Replacement pages are enclosed for the title page and pages 2, 8a - b, 18 - 20, 26, 27, 30 - 32, 32b - c, 33, 35, 38, 39 and 41, 56, the Breast Cancer Prestudy Form (Form #62170) and the Registration Form (Form #13262) are included for insertion into the protocol. The title page reflects the date of this revision.

This memorandum serves to inform the Southwest Oncology Group Statistical Center and the NCI.

cc:	PROTOCOL & INFORMATION OFFICE Stephanie Green, Ph.D. Danika Lew, M.A. Caroline Jiang, M.S. Diana Lowry Karin Rantala Jean Barce	Stephanie Edwards Gity Nasim/EMMES Juanita Tejada/CTSU Debra Litwak/Amgen Col. Julie Zadinsky - DOD Karen Stotler - DOD
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Southwest Oncology Group

A National Clinical Research Group

Distribution Date: October 1, 2002

CTEP Submission Date: September 23, 2002

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CTSU

FROM: Deepa P. Sahrawat, M.P.H., Protocol Coordinator

RE: **S0012**, "A Comparative Randomized Study of Standard Doxorubicin And Cyclophosphamide Followed by Weekly Paclitaxel Vs. Weekly Doxorubicin And Daily Oral Cyclophosphamide Plus G-CSF Followed by Weekly Paclitaxel As Neoadjuvant Therapy For Inflammatory And Locally Advanced Breast Cancer". Study Coordinators: Drs. G. Ellis, R. Livingston, M. Slovak, Ph.D., and Drs. W. Stock and K. Albain.

AMENDMENT #2

Study Coordinator: Georgiana K. Ellis, M.D. Phone: 206/288-2048
Email: gellis@u.washington.edu

IRB Review Requirements

- () Full board review required. Reason:
() Initial activation (should your institution choose to participate)
() Increased risk to patient
() Complete study redesign
() Addition of tissue banking requirements
() Study closure not built into study design
- () Expedited review allowed
() No review required

AMENDMENT #2

The above-noted study has been revised to add paclitaxel to both treatment arms. Additionally, the requirement that patients with locally advanced breast cancer be estrogen-receptor negative has been removed. Specific changes are listed below:

1. The title of the protocol has been revised. The new title, "**S0012**, A Comparative Randomized Study of Standard Doxorubicin and Cyclophosphamide Followed by Weekly Paclitaxel Vs. Weekly Doxorubicin and Daily Oral Cyclophosphamide Plus G-CSF Followed by Weekly Paclitaxel as Neoadjuvant Therapy for Inflammatory and Locally Advanced Breast Cancer", has been updated on the title page, the study calendars 9.1 and 9.2, the first page of the Model Informed Consent and the **S0012** Registration Form (Form #11138). Also, Caroline Jiang, M.S. replaces Danika Lew, M.A. as the secondary statistician for this study and the e-mail addresses for both statisticians have been updated. The page numbering for the appendix has been corrected to read "56a".

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2. The schema on page 2 and in the "What is Involved In This Study?" section of the Model Informed Consent have been revised to include the paclitaxel treatment.
3. Paclitaxel has been added to the agents list on the table of contents page and a drug information section for paclitaxel has been inserted as a new Section 3.4. The rest of Section 3.0 has been renumbered accordingly.
4. The second paragraph on page 6 has been revised to include background information. Four new paragraphs have been inserted after the last paragraph on page 6 (before Table 1) to provide justification for the addition of paclitaxel to the treatment regimen used in this study. Finally, two additional background paragraphs have been inserted on page 8 just before the correlative studies information begins.
5. The last sentence of Section 5.1 has been deleted as it is no longer a requirement that patients with locally advanced breast cancer be estrogen-receptor negative.
6. Sections 7.2 and 7.3 have been revised to include paclitaxel treatment. Section 7.2 has been corrected to specify that paclitaxel treatment will begin three weeks after the last AC dose. Section 7.3 has been revised to indicate that G-CSF will now be given for 16 weeks rather than 15 weeks. Study Calendars, Sections 9.1 and 9.2 have been revised to include the paclitaxel treatment. Also, in Section 9.2, a " ∞ " footnote has been added next to the last "X" in the filgrastim treatment row to specify that filgrastim will now be given for 16 weeks rather than 15 weeks.
7. A new Section 8.4 has been inserted to provide dose modification instructions for paclitaxel treatment. The rest of the section has been renumbered accordingly. Also, the CTEP homepage address has been updated in Section 8.1.
8. The statistical section (Section 11.0) has been updated to reflect the changes made in patient population and protocol treatment with this amendment. Specifically, the considerations have changed from 150/arm to have power to detect .1 vs. .25 in probability of PCR to 175/arm to have power to detect .15 vs. .3 in probability of PCR.
9. Sections 13.3 and 14.3 have been updated to include new Southwest Oncology Group standard language.
10. The first paragraph under "Why Is This Study Being Done?" and the second, third and fourth paragraphs under "What is Involved in This Study?" in the Model Informed Consent have been revised to include the paclitaxel treatment.
11. The number "15" has been replaced with the number "27" in the eighth paragraph of the What is Involved in This Study?" section of the Model Informed Consent as it will now take longer for patients to complete protocol treatment. The risks of paclitaxel treatment have been added to the "What Are The Risks of The Study?" section.

12. The S0012 Assessment Form (Form #4072) has been replaced with the S0012 AC Assessment Form (Form #23540) and the S0012 Paclitaxel Assessment Form (Form #6644). These forms have been inserted in Section 18.2 as items 18.2c and 18.2d. Data submission instructions for these forms have been inserted into Sections 14.7 and 14.16 and into a new Section 14.9. The rest of Section 14.0 has been renumbered accordingly.
13. The former S0012 Assessment Form (Form #4072) has been removed as item "b" from Section 14.6 and the section has been renumbered accordingly. The title of Section 14.8 has been revised to read, "WITHIN 14 DAYS OF DISCONTINUATION OF AC CHEMOTHERAPY."
14. A note has been added to Section 14.11 (formerly 14.10) regarding documentation if surgery is not performed. Section 14.16 (formerly 14.15) has been revised to include instructions for the new forms in the event of death.
15. The prior S0012 Dose Form - Arm 1 (Form #23840) and the prior S0012 Dose Form - Arm 2 (Form #53865) have been replaced with new forms. The S0012 Paclitaxel Dose Form - Arm 1 and Arm 2 (Form #30365) has been added as new item 18.2g and submission instructions for the form inserted into the new Section 14.9. Section 18.0 has been renumbered as necessary.
16. In Section 15.3, Vicki Bedell replaces Margaret Lo. In Section 16.0, the Adverse Event Reporting for CTSU investigators has been updated.

Replacement pages are enclosed for the title page, pages 3, 4, 6, 6a, 8, 8a, 14 - 15b, 17, 19 - 20a, 21, 25 - 32b, 35, 38 - 43a, the S0012 Registration Form (Form #11138), the S0012 AC Assessment Form (Form #23540), the S0012 Paclitaxel Assessment Form (Form #6644), the S0012 Dose Form Arm 1 (Form #40274), the S0012 Dose Form Arm 2 (Form #32573) and the S0012 Paclitaxel Dose Form - Arm 1 and Arm 2 (Form #30365) for insertion into the protocol. Pages 6a, 8a, 15a - b, 20a, 25a - b, 35 and 43a were added to prevent extensive repagination. Please attach this memorandum to the front of your copy of the protocol. The title page reflects the date of this revision.

This memorandum serves to inform the Southwest Oncology Group Statistical Center and the NCI.

cc: PROTOCOL & INFORMATION OFFICE
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December 15, 2001

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CTSU

FROM: Tamra N. Oner, Protocol Coordinator

RE: **S0012**, "A Comparative Randomized Study of Standard Doxorubicin And Cyclophosphamide Vs. Weekly Doxorubicin And Daily Oral Cyclophosphamide Plus G-CSF As Neoadjuvant Therapy For Inflammatory And Estrogen-Receptor Negative Locally Advanced Breast Cancer". Study Coordinators: Drs. G. Ellis, R. Livingston, M. Slovak, Ph.D., and Drs. W. Stock and K. Albain.

AMENDMENT #1

Study Coordinator: Georgiana K. Ellis, M.D. Phone: 206/288-2048
Email: gellis@u.washington.edu

IRB Review Requirements

- () Full board review required
- () Expedited review allowed
- () No review required

AMENDMENT #1

The above-noted study has been revised to include clonal hematopoiesis correlative studies. Specific changes are listed below:

1. Per Central IRB requirements, the title has been modified on the face page, the study calendars 9.1 and 9.2, the first page of the model informed consent, the **S0012** Registration Form (Form #54412) and the beginning of appendices 19.1 - 19.3. Specifically, the phrase "A Randomized Comparison" has been replaced with "A Comparative Randomized Study." Also, study coordinators for the clonal hematopoiesis correlative studies, Marilyn Slovak, Ph.D., Wendy Stock, M.D. and Kathy S. Albain, M.D., have been added to page 2.
2. New objectives 1.5 and 1.6 have been inserted into Section 1.0.
3. Additional background information, titled "Correlative Studies to Determine Frequency of Clonal Hematopoiesis", has been inserted into Section 2.0 prior to the "Inclusion of Minorities" paragraph.
4. The supplier information for filgrastim has been updated in Section 3.3c and the G-CSF order form has been replaced with a new version in Appendix 19.2.

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5. A new Section 5.12 has been inserted to specify that for patients who consent to the clonal hematopoiesis sample submission, prestudy specimens must be submitted as described in Section 15.0. The rest of the section has been renumbered accordingly.
6. The "****" footnote under the table in Section 7.3 has been revised to include the use of dapsone as an alternative for patients unable to tolerate trimethoprim sulfa.
7. The second paragraph of Section 7.5 has been revised to clarify that further treatment after surgery (radiation or additional chemotherapy) is allowed and is per the treating physician. Also, a parenthetical statement, "(See Appendix 19.6)" has been inserted at the end of this paragraph and a separate note has been added to the end of the section specifying that pre-surgical blood samples are to be submitted per Sections 14.9 and 15.0 for patients who consent to the clonal hematopoiesis sample submission.
8. A new item titled "Blood samples for clonal hematopoiesis" has been inserted in the "Laboratory" section of the study calendars, Sections 9.1 and 9.2, and a "¶" footnote inserted which states "For patients who consent to clonal hematopoiesis sample submission, see Section 15.0." The "§" footnote has been revised to state "Adjuvant treatment after post-chemotherapy surgery is at the physician's discretion. Post-surgery therapy must be documented on the Follow-Up Form (Form #61519). (See Appendix 19.6)." Two sentences have been added to the "√" footnote to specify that after one year, patients will be followed by physical exam annually for four more years and any occurrences of leukemia or MDS during that time must be recorded.
9. A new paragraph has been inserted into Section 11.0 to provide statistical considerations for the clonal hematopoiesis correlative studies.
10. Section 14.11 has been revised to require submission of the Southwest Oncology Group Follow-Up Form (Form #61519) annually for up to four more years after the first year of follow-up. Also, a statement has been added to this section which states, "Post-surgery therapy must be documented on the Follow-Up Form (Form #61519). (See Appendix 19.6)". New sections 14.5, 14.9 and 14.12 have been inserted to provide submission instructions for the clonal hematopoiesis blood specimens. The rest of the section has been renumbered accordingly.
11. Section 15.0 has been inserted to provide specific specimen handling and shipping instructions for the clonal hematopoiesis samples.
12. Additional references (#28 - #65) have been inserted at the end of Section 17.0.
13. The Southwest Oncology Group Specimen Submission Form (Form #1951) has been inserted as a new Section 18.2i.
14. A new second paragraph has been inserted into the model informed consent under "Why Is This Study Being Done?" to provide information about the clonal hematopoiesis testing.

15. A new paragraph has been inserted into the model informed consent under "What Is Involved In This Study?" to provide specific information about the timing of specimen submission and the laboratories for the correlative studies. Also, a sentence has been added to the eighth paragraph in this section regarding follow-up in the event of secondary malignancy.
16. A paragraph has been added to the model informed consent regarding the possible risks of venipuncture in the "What Are The Risks Of The Study?" section.
17. A new third paragraph has been inserted into the model informed consent under "Are There Benefits To Taking Part In the Study?" regarding the clonal hematopoiesis testing.
18. A new paragraph regarding ways of determining genetic damage in cells has been inserted into the model informed consent in the "What Other Options Are There?" section.
19. A new second paragraph has been added to the model informed consent in the "What About Confidentiality?" section providing information regarding data storage. Also, a sentence which states "Additionally, if you agree to submit samples for clonal hematopoiesis testing, the U.S. Army Medical Research and Material Command may inspect your research records." has been inserted into the third paragraph of this section. The first sentence of the wording for CTSU investigators has been updated in this section.
20. A new paragraph has been added to the model informed consent in the "What Are The Costs?" section regarding care for venipuncture.
21. A new paragraph and second signature line has been inserted in the "Signature" section of the model informed consent for providing consent for submission of the clonal hematopoiesis samples.
22. A space has been inserted into both participant signature blocks of the model informed consent for the participant to print their name. Also, a signature block has been added underneath both patient signature blocks for a witness to print their name, sign and date the form.
23. A new Appendix 19.5 has been added to the protocol that includes specific information regarding the clonal hematopoiesis assays. A new Appendix 19.6 has been inserted providing information for collecting post-surgical data.

Replacement pages are enclosed for the title page and pages 2, 4 - 6, 8 - 8b, 14, 18, 20 - 21a, 26 - 27, 29 - 32c, 37 - 47, 56a, 57, 62 - 63, 66 - 67, the **S0012** Registration Form (Form #54412) and the Southwest Oncology Group Specimen Submission Form (Form #1951). Pages 8a - b, 14, 21a, 32a - c, 37a - c, 42a, 56a have been inserted to prevent extensive repagination. The title page reflects the date of this revision. Please attach this memo to the front of your copy of the protocol and insert the replacement pages.

This memorandum serves to inform the NCI, EPP institutions, CTSU and the Southwest Oncology Group Statistical Center.

cc:	PROTOCOL & INFORMATION OFFICE Stephanie Green, Ph.D. Danika Lew, M.A. Sheryl Giarritta, M.S. Caroline Jiang, M.S. Diana Lowry Karin Rantala	Jean Barce Stephanie Edwards Gity Nasim/EMMES Juanita Tejada/CTSU Jennifer Tam/Amgen Col. Julie Zadinsky - DOD Karen Stotler - DOD
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May 1, 2001

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP AND AFFILIATE MEDICAL
ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS;
CTSU

FROM: Tamra N. Oner, Protocol Coordinator

RE: **S0012," A Randomized Comparison of Standard Doxorubicin And Cyclophosphamide Vs. Weekly Doxorubicin And Daily Oral Cyclophosphamide Plus G-CSF As Neoadjuvant Therapy For Inflammatory And Estrogen-Receptor Negative Locally Advanced Breast Cancer, Phase III".** Study Coordinators: Drs. G. Ellis and R. Livingston

STATUS NOTICE

Study Coordinator: Georgiana K. Ellis, M.D. Phone: 206/288-2048
Email: gellis@u.washington.edu

IRB Review Requirements (If you choose to participate in this study)

- () Full board review required
() Expedited review allowed
() No review required

ACTIVATION

The study referenced above is now open for patient accrual.

This memorandum serves to inform the NCI, EPP institutions, CTSU and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Stephanie Green, Ph.D.
Danika Lew, M.A.
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PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY
Amended 12/15/01

Amended 9/23/02
Revised 4/1/04
Amended 4/22/04

S0012
Activated May 1, 2001
Revised 5/14/04

SOUTHWEST ONCOLOGY GROUP

A COMPARATIVE RANDOMIZED STUDY OF STANDARD DOXORUBICIN AND CYCLOPHOSPHAMIDE FOLLOWED BY WEEKLY PACLITAXEL VS. WEEKLY DOXORUBICIN AND DAILY ORAL CYCLOPHOSPHAMIDE PLUS G-CSF FOLLOWED BY WEEKLY PACLITAXEL AS NEOADJUVANT THERAPY FOR INFLAMMATORY AND LOCALLY ADVANCED BREAST CANCER

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PARTICIPANTS: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CTSU	

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AGENTS:

Doxorubicin (Adriamycin[®])(NSC123127)
Cyclophosphamide (Cytoxan[®]) (NSC26271)
Filgrastim (r-metHuG-CSF) (NSC-614629)
Paclitaxel (Taxol[®]) (NSC 673089)
Trimethoprim Sulfa (Bactrim[®])

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CLINICAL TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION:

For patient enrollment or to report adverse events:

Phone: 1/888-462-3009
Fax: 1/888-691-8039

To mail forms or data

Westat
CTSU Data Operations Center
1441 West Montgomery Avenue
Rockville, MD 20850-2062

All other questions (including forms - specific questions) should be communicated by phone or e-mail to:

CTSU General Information line: 1/888-823-5923
or ctsucontact@westat.com

All calls and correspondence will be triaged to the appropriate CTSU representative.

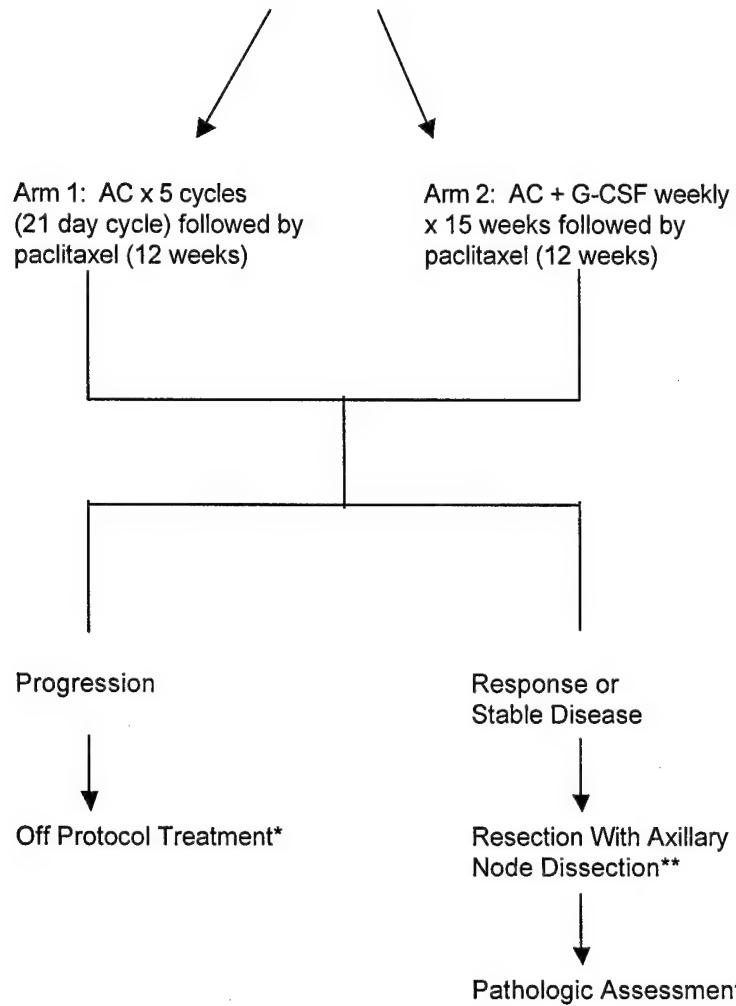
The CTSU public website is located at: www.ctsu.org

The CTSU member website is located at: <http://members.ctsu.org>

Please refer all questions regarding chemotherapy treatment or dose modifications to Dr. Ellis.

SCHEMA

REGISTRATION/RANDOMIZATION



*After progression and removal from protocol treatment, further therapy is per treating physician's discretion.

**After resection with node dissection, further therapy per treating physician's discretion.

1.0 OBJECTIVES

- 1.1 To compare the microscopic pathologic response rates in patients with inflammatory and locally advanced breast cancer treated with weekly doxorubicin and daily oral cyclophosphamide given with G-CSF support followed by weekly paclitaxel for 12 weeks to that in patients treated with the "standard" doxorubicin and cyclophosphamide regimen given every three weeks followed by weekly paclitaxel for 12 weeks.
- 1.2 To compare the toxicities of these two regimens.
- 1.3 To compare the delivered dose intensity of these two regimens.
- 1.4 To assess the association between microscopic pathologic complete response and clinical complete response at the primary tumor site in these patients.
- 1.5 To estimate the incidence of early genetic damage during the course of treatment using two general clonal assays: a) the HUMARA (human androgen receptor assay) to screen for the presence of clonal hematopoiesis, and b) microsatellite instability (MSI) assays to screen for the presence of defective DNA mismatch repair mechanisms and loss of heterozygosity, in pretreatment blood and three sequential post-treatment specimens in breast cancer patients enrolled in this study.
- 1.6 To estimate the incidence of MLL (myeloid lymphoid leukemia) gene fusion transcripts and the frequency of RAS gene mutations (H-, K-, and N-RAS) in cases where either the HUMARA or microsatellite repeat assays are positive for clonal hematopoiesis.

2.0 BACKGROUND

Seminal work by Hryniuk, et al. has suggested that the dose intensity of chemotherapy (the amount of drug per square meter of body surface area per week) correlates with response rate and survival in advanced breast cancer and with relapse-free survival in the adjuvant setting, both for CMF (cyclophosphamide, methotrexate, 5-fluorouracil) and CAF (cyclophosphamide, doxorubicin, 5-fluorouracil) type regimens. (1, 2) Further, in those limited studies where necessary data are available, the use of actual doses delivered, rather than the intended doses specified in the various regimens, results in stronger correlation with outcome for metastatic disease. (3) There are too few adjuvant studies reporting dose delivery to allow such analysis in the adjuvant setting. Although controversial, such analyses have spurred ongoing interest in and evaluation of dose intensity. (4)

The Southwest Oncology Group has reported extensively on a continuous, or "Cooper-" type, CMF regimen in the setting of adjuvant chemotherapy for node-positive breast cancer, in which cyclophosphamide is administered orally on a daily basis and the 5-FU and methotrexate are given by weekly intravenous injection. The Southwest Oncology Group regimen also contains two additional drugs, vincristine and prednisone (CMFVP), and favorable 10 year and 20 year results have been reported with this combination. (5, 27) A Cancer and Leukemia Group B study, however, failed to identify a benefit to the additional two drugs (VP) in the adjuvant setting. (6)

Since the inception of regimens of this type, doxorubicin was developed and found to be one of the most active drugs in metastatic breast cancer, especially hormone-receptor negative disease. Combination chemotherapy regimens that included this drug repeatedly resulted in higher response rates than regimens that did not. Several adjuvant trials have also suggested greater efficacy. (7, 8) A common regimen of this type employs cyclophosphamide, doxorubicin, and 5-fluorouracil administered intravenously every three weeks. As there is potentially greater toxicity with the use of doxorubicin, many practitioners reserve the adjuvant use of this drug for patients with breast cancer at relatively high risk of relapse. The NSABP has reported a comparison between "classical" CMF administered for six months duration and short-course (12 week)

doxorubicin/cyclophosphamide, with comparable outcomes. (9) This would suggest increased efficacy for the use of doxorubicin in combination regimens, given the shorter duration of therapy on this arm. A subsequent study in our group along with ECOG of one year of CMFVP versus 20 weeks of FAC-M (5-fluorouracil, doxorubicin, cyclophosphamide, methotrexate) for receptor negative, node positive primary breast cancer showed no difference in overall survival between the two arms, though disease-free survival was marginally superior ($p=0.06$) on the CMFVP arm. (10)

Investigators at the University of Washington have obtained pilot toxicity data on a "weekly continuous FAC" regimen, modeled after Southwest Oncology Group-type CMF, but with the substitution of doxorubicin for methotrexate, in high risk Stage II and III breast cancer patients, administered as adjuvant and neoadjuvant therapy. (11) The intent of the regimen was to maximize dose intensity. In the first 29 patients treated, delivered dose intensity was 1.21 to 1.24 times higher than seen with two standard "FAC" regimens. Neutropenia was dose-limiting. A subsequent study added continuous daily G-CSF overlapping oral cyclophosphamide to overcome this limitation (see Table 1). (15) Pneumocystis pneumonia was seen in 2 of the first 7 patients treated. Prophylactic trimethoprim sulfa (Bactrim[®]) was added, and an additional two cases were seen in the next 65 treated patients, both of whom had discontinued their Bactrim[®] without notifying investigators.

Thrombocytopenia (platelets below 100,000) occurred in 5% without versus 26% with concurrent G-CSF who received higher chemotherapy doses, and platelets below 50,000 occurred in 0% versus 5% (also received higher chemotherapy doses). No patient required platelet transfusion. Hand-foot syndrome occurred in 9% of patients without G-CSF versus 74% in those who received higher chemotherapy doses with its administration. This was the most common indication for dose delay in the concurrent growth factor study. This pilot trial was supported by Amgen, Inc. (Thousand Oaks, California) under an investigator-initiated IND from the Food and Drug Administration (BB 4482).

With the high incidence of hand-foot syndrome, the widespread use of the NSABP "AC" combination in the treatment of breast cancer, and the desire to dose intensify Adriamycin in the regimen, University of Washington investigators next examined weekly Adriamycin with daily oral cyclophosphamide and G-CSF. Phase I dose escalation of Adriamycin proceeded to 24 mg/m²/week. In the first 37 patients there was one admission for neutropenic fever at this dosing level, and hand-foot syndrome was much decreased, to approximately 24%. Delivered dose intensity of Adriamycin appears to be in the 20 - 22 mg/m²/week range, as compared to 18.1 mg/m²/week for FAC + G. Preliminary experience suggests a "gross complete response" rate nearly twice as high as that seen for FAC + G. This study was also supported by Amgen under the same IND (BB 4482).

Expanded Phase II data on this regimen as neoadjuvant treatment for locally advanced breast cancer were obtained in the Southwest Oncology Group. S9625 accrued 122 patients over a two year period, of which 96 were eligible at the time of evaluation. Median delivered dose of Adriamycin was 21.8 mg/m²/week. No treatment related deaths occurred. Dose limiting toxicity was hematologic: Grade 4 neutropenia in 13 patients, Grade 3 in 46. No febrile neutropenia was seen. Other Grade 4 toxicities included herpetic encephalopathy (1), diarrhea (1) and hematuria (1). In locally advanced breast cancer, combined rates of pCR (pathologic or "microscopic" complete response) and mCR (macroscopic CR, or no gross evidence of residual tumor at pathologic evaluation), pCR alone, and nodal status after neoadjuvant therapy have all been reported as prognostic for disease-free and overall survival. In S9625, pathologic endpoints were evaluable in 88 patients, of whom 37 (42%) met pathologic response criteria with microscopic complete response (pCR) in 23/88 (26%). Among 84 patients who underwent node dissection, 25 were N0. The proportion with pCR+N0 was 21%. This compares to the pathologic CR and macroscopic CR combined of 39%, and pCR alone of 12%, from combined experience of others, primarily in non-inflammatory disease, all in single institution studies. The largest comparable experience is from MD Anderson, reported by Kuerer, of 372 patients with locally advanced, non-inflammatory disease, treated on two Adriamycin-based neoadjuvant regimens, with a combined pCR and mCR rate of 16%, 12% of the total also node negative. (25)

In **S9625**, results appear especially encouraging for patients with inflammatory breast cancer, with 12/49 (24%) pCR, and 22/49 (45%) with pCR+mCR. Similarly encouraging are the respective results in ER-negative disease, with pCR in 16/45, or 36%. This confirms the report from MD Anderson that pathologic complete response was more likely to be seen in patients with ER-negative disease, a relationship first speculated upon by Livingston. (25, 26) We believe these results justify comparison, in this present study, of AC+G to "standard" AC (60/600 q3w) in patients with locally advanced breast cancer.

Using the criteria that were specified in **S9625** under Statistical Considerations, the combined incidence of macroscopic CR and pathologic CR meets the required level of interest for disease that was defined as inflammatory. Among 45 patients currently considered as fully eligible, there were 21 mCR + pCR (47% of all entered, 51% of those who underwent resection), and a response probability of 0.4 had been required to be of interest. For patients defined as non-inflammatory, the observed response rate does not meet the level required for interest (26% of all entered, 31% of those who underwent resection). Further evaluation of the pilot data by hormone receptor status resulted in very similar results in ER-negative patients, where 12/28, or 43%, achieved a pathologic complete response with AC+G in **S9625**. The magnitude of complete pathologic response was not as large in ER-positive patients. However, we believe optimum accrual in these high-risk patients often requires clinical decision to be made prior to hormone results being available. Certainly, the results in **S9625** for ER-positive patients were at least as good as those seen in other studies, with 4/23, or 17% of patients achieving pathologic complete response in the group with locally advanced disease (not inflammatory), positive for estrogen receptor. Although this is a small subset in this study with 103 eligible and evaluable patients, it suggests results at least equivalent to those seen in NSABP B-18 for patients with operable breast cancer.

For the present Phase III trial, because pCR seems to be a much more readily defined criterion than mCR, we proposed Statistical Considerations to consider only pCR as the main endpoint. Adopting the most conservative definition of denominator (all patients entered = 45) in the inflammatory group, there were, in **S9625**, 11 pCR (24%). If we assume that the pCR rate for inflammatory patients receiving "standard" AC is the same as that reported by NSABP for resectable patients in B-18, it would be 13%. We reiterate that NSABP B-18 was a trial largely (90%) of Stage II patients. It seems very unlikely that AC would be as effective in inflammatory disease as in operable disease, but no historical data exist for the inflammatory group. We believe it is realistic to expect a pCR rate of 10% for AC and of 25% for AC+G in the Phase III trial, which would give us a need for about 110 patients in each group. Our statistician recommended rounding upward to 150 patients per arm.

The NSABP has used four cycles of their AC regimen as adjuvant therapy, and four cycles as neoadjuvant in NSABP B-18. But eligibility for B-18 included having "operable" breast cancer, nearly all of which was clinical Stage I or II disease. MD Anderson has reported using 4 - 7 cycles of FAC chemotherapy, with treatment to maximum response. Since it is difficult to specify maximum response in a cooperative group setting, we elected in **S9625** to treat for a specified period of 16 weeks. In fact, average delivered duration of therapy was 15 weeks. We therefore feel, in parallel with our previous Southwest Oncology Group Phase II experience with AC+G, that the comparison of 5 cycles of standard NSABP AC regimen with 15 weeks of the dose-intense AC+G regimen is most appropriate. This is the more investigational component of this study.

Since this study was originally conceived, preliminary information has become available on prolonging neoadjuvant therapy in breast cancer to include the use of a taxane. The largest such study is NSABP B-27, preliminary information from which was presented at ASCO in 2002. B-27 accrued 2,411 patients with clinical stage 1 and stage 2 breast cancer to a three-way randomization: neoadjuvant ACx4, surgery, then taxotere x 4; neoadjuvant ACx4, taxotere x 4, then surgery; and neoadjuvant ACx4 alone followed by surgery. Combining the two neoadjuvant AC arms, the pathologic response rates were 25.6% for patients who received AC followed by docetaxel, compared with 13.7% with AC alone. As in B-18, pathologic response was assessed only in patients achieving complete clinical response.

The Aberdeen study, also presented at ASCO 2002, also evaluated the addition of taxotere to neoadjuvant treatment. Patients with evidence of clinical response to four cycles of CVAP chemotherapy were randomized to either receive another four cycles of the same therapy or, alternatively, receive four cycles of docetaxel. Patients who received docetaxel had a significantly higher clinical response (95% vs. 66%) and complete pathological response (34% vs. 18%). The three-year survival rate was also higher, although not statistically significantly so. Initial pathologic response data from this study was presented at San Antonio in 2000 (Smith).

Further, Green from MD Anderson updated information from a neoadjuvant trial at that institution evaluating q3w paclitaxel versus weekly paclitaxel (Am Soc Clin Oncol abstracts 21:2002, #135, p. 35a). When analyzed by treatment schedule (wkly vs. Q 3 wk), 34 pts treated with wkly P (28.8%) had a pCR (breast and N) when compared to 16 pts (13.6%) receiving the Q 3 wk regimen ($p < 0.01$), with pCR defined as absence of invasive cancer in the breast and lymph nodes.

We believe S0012 as initially formulated has accrued slowly due to the generalized conviction that neoadjuvant chemotherapy for locally advanced breast cancer should ideally include a taxane. We believe weekly taxol is better tolerated than q3w taxotere, and have selected this as our taxane of choice. Whether this will prove to be optimal taxane therapy awaits results of adjuvant E1199 trial. A parallel study running at the University of Washington administers AC+G for 12 weeks, followed by 12 weeks of weekly taxol. To date, 14 patients have completed the AC portion of the protocol and at least two week of Taxol. One patient experienced Grade 4 neutropenia; one patient had an allergic reaction, one patient had persistent Grade 3 hand/foot syndrome, and one patient had Grade 3 nausea/esophagitis requiring IV fluids. No other Grade 3 or higher toxicities were seen. Because of the single grade 4 neutropenia, we have added one additional week of G-CSF to the schedule with initiation of taxol chemotherapy.

Table 1.

Delivered Dose Intensity of Adjuvant Breast Cancer Chemotherapy Regimens
Containing 5-Fluorouracil, Doxorubicin and Cyclophosphamide

	MDAH FAC (13, 14)	ECOG CAF (12)	Continuous FAC (11) (RDI*)	Continuous FAC + G-CSF(15) (RDI*)
5-fluorouracil	267	175	242 (0.91/1.38)	270 (1.01/1.54)
doxorubicin	13.3	10.5	13.2 (0.99/1.26)	19.8 (1.49/1.89)
cyclophosphamide	133	245	250 (1.88/1.02)	414 (3.11/1.69)
adjusted cyclophosphamide**	133	221	225 (1.69/1.02)	373 (2.80/1.69)
RDI, *** regimen	1.00	1.09	1.26	1.87
RDI, *** regimen, adjusted	1.00	1.04	1.20	1.77

* RDI = Relative dose intensity, continuous weekly FAC or continuous weekly FAC + G-CSF vs. other. This is the delivered dose intensity of each agent of our regimen (without and with G-CSF) divided by that from the reported reference regimens (MDAH FAC, ECOG CAF).

** Bioavailability based on 90% absorption of oral cyclophosphamide.

*** RDI, average of each of the three drugs divided by MDAH FAC as reference regimen, as per the method of Hryniuk, who did not adjust for the oral bioavailability of cyclophosphamide. Presented, American Society of Clinical Oncology, May 1994, Dallas, Texas.

Table 2 reviews the published results from eight trials of neoadjuvant chemotherapy in locally advanced breast cancer. It is of note that the reported range of observed clinical complete responses is very broad, from 4 to 49%. The likelihood of observing a clinical complete response appears related to initial tumor size, and was as high as 71% for FAC with T2 tumors as reported in Hortobagyi's series. (16) Of perhaps greater interest is the poor correlation of clinical assessment of response compared to pathologic assessment for the few studies in which this was reported and the fact that the correlation can be poor in either direction. For example, the McCready study, also at M.D. Anderson, reported a higher pathologic than clinical complete response rate, though in most reports of primary chemotherapy for operable breast cancers the discordance has been in the opposite direction. (17) Swain's series (the Georgetown experience) is the most impressive, with a pathologic complete response rate estimated at 30% (62% of the 49% who had clinical complete responses). (18) This study employed CAMF with "hormone synchronization." Our expectation would be that higher delivered dose intensity would improve upon these results.

Table 2.

Neoadjuvant Chemotherapy in Locally Advanced Breast Cancer

Reference	Number of Patients	Induction Regimen	Duration (cycles)	Clinical CR	RR Overall	Path CR
De Lena (19)	74	A + VLB		14	73	
De Lena (20)	132	A + VLB		4	52	
Lesnick (21)	99	CMFpV		18	72	
Jacquillat (22)	98	FAVThMp		23	91	
McCready (17)	136	FAC	3 - 6	13	87	23*
Swain (18)	76	CAMF**	3 - 5	49	93	30 (est)
O'Reilly (23)	21		4	33	86	
Hortobagyi (16)	100	VCR + ACP	3	19 (13 - 71)	89	

*No gross tumor, with or without microscopic complete response.

**Plus "hormonal synchronization" with tamoxifen and Premarin.

In those series which have reported on pathologic response and its correlation with clinical outcome, the most important variable has been achievement of a macroscopic complete response (CR) (no visible or palpable remaining tumor, with or without microscopic residual). For example, in McCready's series from MDAH, patients who achieved a macroscopic CR (23% of the total) had a 65% five-year survival, compared to a five-year survival of 49% in the remainder who had gross residual ($p = 0.03$). (17) No difference in outcome was cited between gross and microscopic CRs. Similarly, Armstrong, et al., from Johns Hopkins reported that the only factor predicting outcome in their neoadjuvant series was pathologic response: at a median follow-up of 45 months, relapse had occurred in 1/11 (9%) patients with macroscopic CR versus 9/13 (69%) with macroscopic residual disease. (24)

Literature in Phase II studies of LABC suggests that outcome is correlated with pathologic response rate. Recently, the NSABP reported improved pCR rates in patients receiving four cycles of taxotere following four cycles of doxorubicin and cyclophosphamide (AC) as neoadjuvant therapy for *operable* breast cancer in NSABP B-27. In groups I and III of that study (approximately 1460 patients), receiving neoadjuvant AC alone, the pathologic complete response rate was 9.8%, with an additional 3.9% without residual invasive disease, or a total of 13.7%, which is comparable to results seen in NSABP B-18. Arm II, of an additional 700+ patients, receiving ACx4 followed by four cycles of taxotere, had rates of 18.7 pCR, 6.9% pInv, or a total of 25.6%. It remains to be seen whether improved overall pCR will correlate with improved primary endpoints; in B-18, there was no difference in DFS and OS in patients receiving pre-operative versus post-operative chemotherapy. However, it appears now that the community standard in neoadjuvant chemotherapy is to include a taxane.

It is not clear which taxane would be optimal. In cross-study Phase III comparisons, docetaxel (TXT) has appeared superior to paclitaxel (TAX) in Stage IV disease. However, Phase II data suggests that weekly taxol may circumvent problems with suboptimal dose and schedule of TAX. Due largely to toxicity concerns, we propose using weekly taxol as the second component of neoadjuvant therapy in this protocol, and adding this treatment to both arms.

Correlative Studies to Determine Frequency of Clonal Hematopoiesis.

As disease-free and overall survival for patients with breast cancer following treatment for breast cancer with anthracycline-based combination chemotherapy continues to improve, concerns relating to late effect complications of therapy must be investigated. Therapy-related myelodysplastic disorders and leukemia (t-MDS/AML) associated with chemotherapy, particularly alkylating agents and topoisomerase II inhibitors, are being reported with increasing frequency in the literature, in particular after breast cancer treatment. (28 - 30) t-MDS/AML evolve as a result of expansion of an abnormal clone of hematopoietic stem cells that have acquired somatic mutations conferring a growth advantage.

According to the Jacobs model for leukemogenesis, the mutations resulting in clonal hematopoiesis may occur without any obvious hematological change (no dysplasia or cytopenias noted). (31) Subsequently, the acquisition of a variety of additional genetic lesions may be essential for the development of MDS (preleukemia) or overt leukemia. Clonal chromosomal abnormalities have been reported in the majority of cases of t-MDS/AML. The most frequently reported abnormalities involve complete loss or interstitial deletions of the long arm of chromosomes 5 and/or 7. Typically, these leukemias develop following alkylating agent-induced damage at a median of 3 - 5 years following therapy. (32) The second group of t-MDS/AML is associated with rearrangements of the *MLL* gene localized to chromosome band 11q23. (33 - 36)

The 11q23-associated t-AMLS often develop following treatment with drugs that target DNA-topoisomerase II (e.g., epipodophyllotoxins, anthracyclines) with a very short (12 to 18 months) latency following treatment. (35)

Over the last ten years, anthracyclines have become a major component of combination chemotherapy regimens for breast cancer. Two adjuvant breast cancer trials, NSABP-B25 and NCIC, employing dose-intensive anthracycline-based chemotherapy, reported rates of t-MDS/AML that are two to four-fold higher than in previous adjuvant studies. (29 - 30) Notably, the most dose intensive arms of these studies employed the use of hematopoietic growth factors to facilitate blood count recovery following the high dose chemotherapy. The leukemias that developed in these patients had a monocytic morphology and occurred following a short latency period (within two years of adjuvant therapy), a characteristic finding of the hematologic disorders linked to the topoisomerase II inhibitors. Cytogenetic analysis revealed rearrangements of 11q23 in five of eight of these cases. (32 - 37) Further concern about the development of t-MDS/AML following high-dose chemotherapy for breast cancer may be warranted based on the alarming data emerging on high rates of development of t-MDS/AML following autologous transplantation for lymphoma, where the incidence of therapy-related leukemias has been estimated to be as high as 18% at six years following transplantation. (38 - 41)

These studies raise three major concerns: 1) Does genetic damage leading to the development of clonal hematopoietic stem-cell disorders occur with unacceptable frequency in patients receiving these intensive anthracycline-based adjuvant regimens for the treatment of breast cancer? (and, accordingly, what frequency is unacceptable?) 2) Will careful monitoring of this patient population reveal additional t-MDS/AML with long-term follow-up? and 3) Does the administration of recombinant hematopoietic growth factors (i.e., G-CSF) used to minimize morbidity and facilitate scheduled drug dosing play a potentiating role in the development of these secondary malignancies? This study will focus on the first concern; in addition, insights into the potential contributing role of hematopoietic growth factors in the induction of genetic damage to hematopoietic stem cells may be gained by comparison of the two treatment arms since only one group will receive G-CSF support.

Chemotherapeutic agents used in the treatment of breast cancer may induce genetic damage. This damage may result in clonal proliferation, which, according to the Jacobs model of neoplasia is an essential early, possibly initial, step in leukemogenesis, occurring prior to the development of clinical abnormalities. (31) Data confirming the presence of clonal proliferation following

chemotherapy exist. Carter and others described clonal hematopoiesis in more than 30% of 70 clinically asymptomatic patients who had received prior cytotoxic chemotherapy for lymphoma. (31, 42 - 43) Busque, et al. found that clonal hematopoiesis existed in 8 of 12 (67%) patients with Hodgkin's or Non-Hodgkin's lymphomas studied prior to autologous transplantation (all had received prior chemotherapy), and that this value was significant ($p < 0.0033$) when compared to normal control donors. (44) Gale et al. have shown that sequential X-linked clonality assays are predictive of subsequent evolution to frank MDS/AML. (45) These provocative studies suggest that the presence of clonal hematopoiesis following chemotherapy may be a relatively common event. Pilot studies are warranted to determine the clinical relevance of these interesting findings.

The development of clonal hematopoiesis may be one of the earliest events that occur in an evolving neoplastic process. (31, 46) Thus, assays to detect clonality, such as the polymerase chain reaction (PCR)-based HUMARA (human androgen receptor assay), may define the primary steps in the evolution to t-MDS/AML. (46, 47) The HUMARA is informative in more than 90% of females and is; therefore, probably the optimal clonality assay for testing female blood or marrow samples for clonal hematopoiesis at regular intervals. (47, 48) Genomic instability at simple repeated DNA sequences, or microsatellites, is a sensitive marker of a genetic damage. (49, 50) It appears that instability in these repeated sequences is a result of defective DNA replication/repair mechanisms. In two recent publications, genomic instability in microsatellite variants arising from genomic instability can be used as clonal markers in hematologic malignancies. (51, 52) Therefore, the microsatellite instability and the HUMARA assays are complementary PCR-based methods of detecting genetic damage, and can be done using a very small amount of DNA obtained from blood. To determine the incidence of specific genetic lesions following anthracycline-based regimens for breast cancer, *MLL* gene rearrangements and *RAS* mutations, genetic alterations frequently observed in therapy-related hematopoietic disorders will be evaluated in those cases where either or both of the general clonality assays show evidence of early genetic damage.

The question that is being asked in this clinical trial is whether more "dose intensive" delivery of Adriamycin and cyclophosphamide may improve upon disease free and overall survival without increasing the risk of developing t-MDS/AML in women with high-risk breast cancer. As part of this study, we would like to determine whether these agents, given in different doses and schedules, induces genetic damage to hematopoietic stem cells, defined by the emergence of clonal hematopoiesis utilizing two different assays (the HUMARA and microsatellite instability). To answer this question and to determine whether this more dose intensive regimen (daily oral cyclophosphamide, weekly Adriamycin and hematopoietic growth factor support) induces genetic damage with a higher frequency than "standard" AC (administered every 21 days without hematopoietic growth factor support), we have chosen to study sequential blood samples from 200 women enrolled on this study (100 per arm). We will evaluate/compare the frequency of clonal hematopoiesis in both standard and dose intensive arms of this study and control for variables such as age or damage that may have occurred due to other risk factors/exposures induced damage by using pretreatment (baseline) samples.

Inclusion of Minorities:

Anticipated accrual by race for this study follows:

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	Total
Female	0	12	20	25	243	0	300

Race-treatment interactions are not anticipated, so the trial has not been powered to address specific race questions. However, we will do exploratory analysis of treatment by race at the end of the study.

3.0 DRUG INFORMATION

3.1 Cyclophosphamide (Cytoxan®) (NSC-26271)

a. DESCRIPTION

2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxidemohydrate. Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites which cross-link to tumor cell DNA.

b. TOXICOLOGY

Human Toxicology: Toxicity from cyclophosphamide includes bone marrow suppression which usually occurs 10 to 12 days after administration, nausea, vomiting, anorexia, abdominal discomfort, diarrhea, stomatitis, hemorrhagic colitis, jaundice, reversible alopecia, hemorrhagic cystitis which can frequently be prevented with increased hydration, hematuria, ureteritis, tubular necrosis, fibrosis of the bladder, cardiac toxicity which may potentiate doxorubicin-induced cardiotoxicity, rare anaphylactic reaction, skin rash, hyperpigmentation of the skin and nails, interstitial pulmonary fibrosis, and cross sensitivity with other alkylating agents. Treatment with cyclophosphamide may cause significant suppression of the immune system.

Second malignancies, most frequently of the urinary bladder and hematologic systems, have been reported when cyclophosphamide is used alone or with other anti-neoplastic drugs. It may occur several years after treatment has been discontinued. It interferes with oogenesis and spermatogenesis and may cause sterility in both sexes which is dose and duration related. It has been found to be teratogenic, and women of childbearing potential should be advised to avoid becoming pregnant. Increased myelosuppression may be seen with chronic administration of high doses of phenobarbital. Cyclophosphamide inhibits cholinesterase activity and potentiates effect of succinylcholine chloride. If patient requires general anesthesia within 10 days after cyclophosphamide administration, the anesthesiologist should be alerted. Adrenal insufficiency may be worsened with cyclophosphamide. Cyclophosphamide is excreted in breast milk, and it is advised that mothers discontinue nursing during cyclophosphamide administration. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

c. PHARMACOLOGY

Kinetics: Cyclophosphamide is activated principally in the liver by a mixed function microsomal oxidase system. PO administration is well absorbed, with bioavailability greater than 75%. Five to twenty-five percent of unchanged drug is excreted in the urine. Several active and inactive metabolites have been identified with variable plasma protein binding. There appears to be no evidence of clinical toxicity in patients with renal failure, although elevated levels of metabolites have been observed.

Formulation: Cyclophosphamide is supplied in 100 mg, 200 mg, 500 mg, 1 gram and 2 gram vials as a white powder. The drug should be reconstituted with Sterile Water for Injection, USP, and may be diluted in either normal saline or D5W. The PO form is supplied as 50 mg and 25 mg tablets.

Storage and Stability: Although the reconstituted cyclophosphamide is stable for six days under refrigeration, it contains no preservatives and therefore should be used within 6 hours. Tablets are stable at room temperature.

Administration: Cyclophosphamide should be diluted in about 150 cc of normal saline or D5W and infused IV. An added dose of IV fluids may help prevent bladder toxicity. The tablet form of the drug may also be administered PO.

Supplier: Cyclophosphamide is commercially available and should be purchased by a third party. This drug will not be supplied by the NCI.

3.2 Doxorubicin (Adriamycin®)(NSC-123127)

a. DESCRIPTION

Mechanism of Action: Doxorubicin is a cytotoxic anthracycline antibiotic different from daunorubicin by the presence of a hydroxyl group in the C-14 position. Doxorubicin is produced by fermentation from *S. Peucetius* var. *caesius*. Its mechanism of action is thought to be the binding of nucleic acids, preventing DNA and possibly RNA synthesis.

b. TOXICOLOGY

Human Toxicology: Studies with doxorubicin have shown that the major toxic effects of this drug are alopecia, which is often total but always reversible; nausea and vomiting, which develops shortly after drug administration, occasionally persisting for 2 - 3 days; fever on the day of administration; and phlebitis at the site of the drug's injection. Extravasation of the drug will lead to soft tissue necrosis. Phlebosclerosis, cellulitis, vesication and erythematous streaking have also been seen. Mucositis may be seen 5 - 10 days after administration. Ulceration and necrosis of the colon, particularly the cecum, with bleeding and severe infection have been reported with concomitant administration of cytarabine. Anorexia and diarrhea have also been observed. Hyperpigmentation of nailbeds and dermal creases, onycholysis and recall of skin reaction from prior radiotherapy may occur. Cardiac toxicity manifested as acute left ventricular failure, congestive heart failure, arrhythmia or severe cardiomyopathy has been reported, but appears to occur predominantly in patients who receive total doses in excess of 550 mg/M². Myelosuppression, predominantly neutropenia, is common with nadir occurring approximately two weeks after a single injection; lesser degrees of anemia and thrombocytopenia have been reported. Rapid recovery of the blood counts approximately two and a half weeks after a single injection generally permits an every three week schedule. Patients with obstructive liver disease have more severe myelosuppression due to impaired drug excretion. Thus, patients with hepatic dysfunction may need to have reduced dosage or to be excluded from therapy. Renal excretion of doxorubicin is minimal, but enough to color the urine red; thus impaired renal function does not appear to increase the toxicity of doxorubicin. Other side effects include fever, chills, facial flushing, itching, anaphylaxis, conjunctivitis and lacrimation. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

c. PHARMACOLOGY

Kinetics: Intravenous administration is followed by a rapid plasma clearance with significant tissue binding. Urinary excretion is negligible; biliary excretion accounts for 40 to 50% of the administered dose being recovered in the bile or the feces in 7 days. The drug does not cross the blood-brain barrier.

Formulation: Doxorubicin is supplied in 10, 20 and 50 mg single-use vials, and 150 mg multidose vials as a red-orange, lyophilized powder which has a storage stability of at least two years - see expiration date on vial. Doxorubicin should be reconstituted with 5, 10, 25 and 75 ml respectively, of Sodium Chloride Injection, USP (0.9%) to give a final concentration of 2 mg/ml.

Storage and Stability: The reconstituted doxorubicin is stable for 24 hours at room temperature and 48 hours under refrigeration (2° - 8°C). It should be protected from exposure to sunlight. Discard any unused solution from the vials. Bacteriostatic diluents with preservatives are NOT recommended as they might possibly worsen the reaction to extravasated drug.

Administration: Doxorubicin may be further diluted in 5% dextrose or sodium chloride injection and should be administered slowly into tubing of a freely flowing intravenous infusion with great care taken to avoid extravasation.

Supplier: This drug is commercially available for purchase by the third party. This drug will not be supplied by the NCI.

3.3 Filgrastim (r-metHuG-CSF) (NSC-614629) (BB-IND-2704)

a. DESCRIPTION

Filgrastim, Neupogen®, recombinant-methionyl human granulocyte-colony stimulating factor, granulocyte-colony stimulating factor, r-methHuG-CSF, is a protein produced by E. coli into which has been inserted the human granulocyte colony-stimulating factor gene. Filgrastim differs from the natural protein in that the N-terminal amino acid is a methionine and it is not o-glycosylated. G-CSF functions as a hematopoietic growth hormone; it increases the proliferation, differentiation, maturation and release of precursor cells into mature blood cells of the neutrophil lineage. G-CSF has demonstrated in vitro effects on mature neutrophils, including an increased expression of chemotactic receptors, enhanced phagocytosis and intracellular killing of certain organisms, as well as enhanced killing of target cells that are bound by antibodies.

Approximately 6,400 patients in U.S. and international based trials have participated in clinical trials of filgrastim to date, and the worldwide commercial populations receiving filgrastim totaled approximately 190,000. The drug has been found to be well tolerated at dosages up to 69 µg/kg/day given IV or SC, with no toxic effects attributable to filgrastim. A maximum tolerated dose has not yet been determined.

Classification: Colony stimulating factor; cytokine.

b. TOXICOLOGY

The most frequently reported adverse effect was medullary bone pain, occurring in 20 - 25% of patients in Phase II and III trials. When bone pain was reported it often preceded a rise in the circulating neutrophil count; it occurred more frequently in patients treated with 20 - 100 µg/kg/day of intravenously administered filgrastim and less often in lower subcutaneous doses. The pain was generally mild to moderate in severity, and usually controlled with non-narcotic analgesics such as acetaminophen. Other side effects include transient but reversible increases of alkaline phosphatase, lactate dehydrogenase and uric acid levels. These occurred in 27 - 58% of patients, without clinical sequelae

observed. Elevations of leukocyte alkaline phosphatase levels have also been noted but the significance is not yet known. Less frequently reported adverse events related to filgrastim administration include subclinical splenomegaly, exacerbation of pre-existing skin rashes, alopecia, and thrombocytopenia, and cutaneous vasculitis. Ischemic or infarcted colon, sometimes with involvement of other parts of the gastrointestinal tract, has been seen in patients receiving paclitaxel and G-CSF therapy. Patients reporting abdominal discomfort should be monitored closely. The specific etiologic role of paclitaxel, other chemotherapeutic agents or G-CSF is not entirely defined. It is conceivable that the high doses of chemotherapy used in these studies induced sufficiently severe neutropenia that these patients were at risk for this complication based on the myelotoxicity alone. If this is the case, then the use of G-CSF may actually assist in preventing this occurrence in other patients receiving high-dose paclitaxel chemotherapy. A review of the Amgen database of over 10,000 patients treated on company-sponsored trials reveal that the occurrence of only one case of typhlitis, two instances of intestinal ischemia, and six occurrences of intestinal perforation. However, it is remotely possible that the G-CSF may have contributed in some unforeseen way to these events.

Rarely, allergic-type reactions have occurred. Since the commercial introduction of filgrastim there have been reports (< 1 in 4,000 patients) of symptoms suggestive of an allergic-type reaction, but in which an immune component has not been demonstrated. These have generally been characterized by systemic symptoms involving at least two body systems, most often skin (rash, urticaria, edema), respiratory (wheezing, dyspnea), and cardiovascular (hypotension, tachycardia). Some reactions occurred on initial exposure. Reactions tended to occur within the first thirty minutes after administration and appeared to occur more frequently in those patients who received filgrastim intravenously. Rapid resolution of symptoms occurred in most cases after administration of standard supportive care, and symptoms recurred in more than half the patients when rechallenged.

Precautions: filgrastim should be used with caution in patients with pre-existing cardiac conditions such as hypertension, angina pectoris and cardiac dysrhythmias. Until further data become available, precaution should be exercised if filgrastim is administered to those patients with myeloid malignancies.

Pregnancy and Lactation: No clinical trials have been performed in pregnant or lactating women. Therefore, administration of filgrastim, (r-metHuG-CSF) during pregnancy or lactation is not recommended until further data are available.

Contraindications: filgrastim is contraindicated in those patients with known hypersensitivity to E. coli-derived proteins.

c. PHARMACOLOGY

Formulation: Recombinant G-CSF, filgrastim, NEUPOGEN®, is supplied as a clear, colorless preservative-free liquid for parenteral administration. Single use vials contain filgrastim 300 µg/ml in a preservative-free solution with 0.59 mg/ml acetate, 50 mg/ml sorbitol, 0.004% Tween® 80, 0.035 mg/ml sodium, and water for injection, USP, pH 4.0 to make 1 ml filgrastim Neupogen® is commercially available in 2 vial sizes: 300 µcg/1 ml and 480 µg/1.6 ml.

Dilution: If required, filgrastim may be diluted in 5% dextrose. Filgrastim diluted to concentrations between 5 and 15 µg/ml should be protected from adsorption to plastic materials by addition of albumin (Human) to a final concentration of 2 mg/ml. When diluted in 5% dextrose or 5% dextrose plus albumin (Human), filgrastim is compatible with glass bottles, PVC and polyolefin IV bags, and polypropylene syringes. Dilution of filgrastim to a final concentration of less than 5 µg/ml is not recommended at any time. Do not dilute with saline at any time; product may precipitate.

Mode of Action: Hematopoietic regulator with effects on both immature bone marrow progenitors and mature myeloid cells; it acts by supporting growth of human bone-marrow-derived, colony-forming units and enhancing neutrophil-mediated, antibody-dependent cellular toxicity.

Storage and Stability: Filgrastim should be refrigerated and not allowed to freeze. It is stable for 24 hours at room temperature if the solution remains clear. At a concentration of 5 mcg/ml or greater in D5W, filgrastim is stable for 7 days at room or refrigerator temperatures. At dilutions from 5 to 14 mcg/ml, albumin in a final concentration if 2 mcg/ml should be added to protect against adsorption. Addition of albumin is unnecessary when the drug is diluted to a concentration greater than or equal to 15 mcg/ml in D5W. Concentrations of less than 5 mcg/ml should not be used. Dilutions in D5W are stable in glass bottles, polyvinyl chloride, polyolefin or polypropylene bags and IV sets, and Travenol Infusors.

Preparation: Draw appropriate dose into syringe for subcutaneous injection.

Incompatibilities: Normal saline.

Side Effects

Musculoskeletal: In clinical trials medullary bone pain was the only consistently observed adverse event attributed to Filgrastim and was reported in approximately 24% of patients across all indications. The bone pain was generally mild to moderate in severity and controllable in most patients with non-narcotic analgesia; infrequently, bone pain was severe enough to require narcotic analgesia.

Cardiovascular: Rarely fluid retention; transient hypotension; pericardial effusion.

Dermatologic: Local inflammation at the injection site; rarely cutaneous vasculitis.

Other: Transient, mild to moderate elevations of uric acid, LDH, alkaline phosphatase and leukocyte alkaline phosphatase when given with cytotoxic drugs.

Nursing Guidelines

Filgrastim should be kept in the refrigerator until needed and the vials should not be shaken.

The drug should be administered at the same time each day. Vials of filgrastim are single-dose and the remaining drug should be discarded.

Refer to protocol for information regarding requirements for documentation of doses administered, temperatures, side effects, etc.

Acetaminophen is the recommended analgesic for mild bone pain.

Duration of therapy will be determined by the return of blood counts (WBC/ANC) to specific values.

Administration: Filgrastim is administered as a single daily injection by SC bolus injection, by short IV infusion (15 - 30 minutes), or by continuous SC or continuous IV infusion.

Supplier: G-CSF (Filgrastim) is commercially available. However, for this study it is being supplied free-of-charge by Amgen, Inc. and is available from Uinta Vision. To obtain a supply of G-CSF, complete the G-CSF (Filgrastim) Drug Request Form supplied in Appendix 19.2, and fax or send the form to:

Uinta Vision Inc./Axion, Inc.
232 Castro Street, Suite #2
San Francisco, CA 94114
General Phone (800) 370-2508
Fax: 650/745-3877

Uinta Vision's office hours are 8:00 a.m. to 1:00 p.m. PST, phone message may be left at other times. Phone messages left after 1:00 p.m. will be returned the next morning.

Orders received by 11:30 p.m. PST Monday through Thursday will be shipped for next day delivery. The initial shipment to each study site will be delivered by 3:30p.m. **G-CSF orders from USA sites only will be accepted.** Patients must be registered to the study before study drug can be obtained.

For this study, G-CSF is supplied in 480 mcg/1.6 ml vials; initial order quantities will be 100 vials; reorder quantities will be in 30 vial increments. Unused drug at the site upon termination of the study will need to be returned to Uinta Vision, Inc./Axion, Inc., with a completed Return Medication Packing Slip (see Appendix 19.3) included identifying for which study the drug was originally shipped.

3.4 Paclitaxel, Taxol® (NSC-673089)

a. DESCRIPTION

Chemistry: Paclitaxel is a diterpene plant product found in the needles and bark of the western yew, Taxus brevifolia. The marketed formulation is prepared in a semi-synthetic process.

Molecular Weight: 853.9

Empirical Formula: C₄₇H₅₁NO₁₄

Description: Clear viscous fluid

b. TOXICOLOGY

Human Toxicity:

Dose-limiting toxicity is myelosuppression with reversible granulocytopenia, anemia, and thrombocytopenia. Allergic reactions occur in up to 8% of patients receiving paclitaxel as an intravenous infusion over 6 to 24 hours. These can be acute anaphylactoid reactions to include flushing, hypotension, and bronchospasm; dermatitis and pruritus are also observed. Hypertension has also been seen, and may be related to concomitant medication with dexamethasone. Premedication with diphenhydramine, cimetidine, and dexamethasone appears to diminish the incidence of these reactions. Neurotoxicity can include distal painful paresthesias. Rarely, this toxicity has required discontinuation of drug due to pain, impairment of fine motor skills, or difficulty ambulating. Experience to date suggests that this neuropathy is reversible. Rarely, associated forms of neurotoxicity have included taste perversion, seizures, and mood changes. Some patients have reported vision abnormalities such as blurred vision, "flashing lights" and scintillating scotomata. Ischemic or infarcted colon, sometimes with involvement of other parts of the gastrointestinal tract, has also been seen. Patients reporting abdominal discomfort should be monitored closely. These events generally occurred while the patients were severely neutropenic. They may be most consistent with neutropenic enterocolitis (typhlitis). Although increased SGOT, SGPT, bilirubin and alkaline phosphatase, as well as hepatic failure and hepatic necrosis have been seen, one patient receiving this drug has also experienced hepatic encephalopathy, and two incidences of pancreatitis have been noted. Neuroencephalopathy has also been reported. Pulmonary toxicities that have occurred are pneumonitis and radiation pneumonitis (following concomitant paclitaxel and radiation).

Other non-hematologic reactions include: diarrhea, alopecia, myalgias and arthralgias, nausea or vomiting, mucositis (stomatitis and pharyngitis), light-headedness, myopathy and fatigue. Less commonly, cardiotoxicity has been associated with paclitaxel administration, to include arrhythmias (sinus bradycardia, ventricular tachycardia, atrial arrhythmia, and heart block), and myocardial infarction. Skin reactions including erythema, induration, tenderness, ulceration, radiation recall, rash and nail changes have occurred including discoloration of fingernails and separation from nail bed.

Pregnancy and Lactation: Paclitaxel may cause fetal harm when administered to a pregnant woman. Paclitaxel has been shown to be embryo- and fetotoxic in rats and rabbits and to decrease fertility in rats. In these studies, paclitaxel was shown to result in abortions, decreased corpora lutea, a decrease in implantations and live fetuses, and increased resorption and embryo-fetal deaths. No information is available on the excretion of this drug in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued.

c. PHARMACOLOGY

Formulation: Sterile solution containing 6 mg/ml in a 5 ml vial (30 mg per vial) in polyoxyethylated castor oil (Cremaphor EL) 50% and dehydrated alcohol, USP, 50%. There are also vial sizes of 100 mg and 300 mg.

Solution Preparation: Paclitaxel is reconstituted by diluting the total dose in 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP (D5W) to maintain a paclitaxel concentration between 0.3 and 1.2 mg/ml. Paclitaxel must be prepared in glass or polyolefin containers due to leaching of

diethylhexylphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremaphor vehicle in which paclitaxel is solubilized. Each bag/bottle should be prepared immediately before administration.

NOTE: Formation of a small number of fibers in solution (within acceptable limits established by the USP Particulate Matter Test for LVPs) has been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtrations should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: IVEEX-II or IVEEX-HP or equivalent) into the IV fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

Administration of Paclitaxel: Paclitaxel, at the appropriate dose, will be given as a continuous IV infusion as specified in the protocol, diluted in 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection. Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and connectors, such as the IV administration sets (polyethylene or polyolefin) which are used to infuse parenteral nitroglycerin. Nothing else is to be infused through the line where paclitaxel is being administered.

Storage and stability: The intact vials of paclitaxel should be stored between 2 - 25°C. Based on stability data for Taxol® made from either natural or semi-synthetic paclitaxel, stored for up to 12 months at 40°C, potency losses were within the range of 2.0 to 2.4 percent per year. Samples stored for up to 3 months at 60°C lost potency at rates corresponding to 20 to 40% per year. Accordingly, vials left out in a warm place for a few days should still be satisfactory for use. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3 - 1.2 mg/ml) are physically and chemically stable for 27 hours. Vials will be labeled with a firm expiration date.

Supplier: Paclitaxel is commercially available for purchase by the third party. This drug will not be supplied by the NCI.

3.5 Trimethoprim Sulfa (Bactrim®)

a. DESCRIPTION

Chemistry: Trimethoprim-sulfa is an anti-bacterial compound which is a combination of a pyrimidine (trimethoprim) together with a sulfonamide (sulfamethoxazole).

b. TOXICOLOGY

Human Toxicity: Human toxicity includes myelosuppression, allergic reactions including erythema multiforme, Stevens-Johnson syndrome, and other dermatitis, mucositis, nausea, vomiting, abdominal pain, hepatitis, headache, mental depression, convulsions, drug fever, chills and toxic nephrosis.

c. PHARMACOLOGY

Microbiology: Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid by competing with para-aminobenzoic acid. Trimethoprim blocks the production of tetrahydrofolic acid and dihydrofolic acid by binding and reversibly inhibiting dihydrofolate reductase. Thus two consecutive steps in the biosynthesis of nucleic acids essential to many bacteria are inhibited.

Human Pharmacology: This drug is rapidly absorbed following oral administration. Blood levels of each component are similar to those achieved when each is given alone. Peak blood levels occur one to four hours after oral administration. Both drugs are present in the blood as free, conjugated, and protein bound forms. Free forms are considered to be therapeutically active drug. Excretion of the compound is chiefly by the kidneys through glomerular filtration and tubular secretion.

Formulation: Tablets containing 80 mg trimethoprim and 400 mg sulfamethoxazole and suspension containing 40 mg of trimethoprim and 200 mg sulfamethoxazole per teaspoon are available. DS (double strength) tablets containing 160 mg trimethoprim and 800 mg sulfamethoxazole are white notched tablets.

Administration: PO.

Supplier: Trimethoprim sulfamethoxazole is commercially available and should be purchased through a third party. This drug will NOT be supplied by the NCI.

4.0 STAGING CRITERIA

DEFINITION OF TNM

Primary Tumor (T)

Definitions for classifying the primary tumor (T) are the same for clinical and for pathologic classification. The *telescoping* method of classification can be applied. If the measurement is made by physical examination, the examiner will use the major headings (T3, T4). If other measurements, such as mammographic or pathologic, are used, the telescoped subsets of T1 can be used.*

- T1 Tumor 2 cm or less in greatest dimension
- T2 Tumor more than 2 cm but not more than 5 cm in greatest dimension
- T3 Tumor more than 5 cm in greatest dimension
- T4† Tumor of any size with direct extension to chest wall or skin.
 - T4a Extension to chest wall
 - T4b Edema (including peau d'orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast
 - T4c Both (T4a and T4b)
 - T4d Inflammatory carcinoma

*Note: Paget's disease associated with a tumor is classified according to the size of the tumor.

†Note: Chest wall includes ribs, intercostal muscles, and serratus anterior muscle but not pectoral muscle.

Regional Lymph Nodes (N)

- N0 No regional lymph node metastasis
- N1 Metastasis to movable ipsilateral axillary lymph node(s)
- N2 Metastasis to ipsilateral axillary lymph node(s) fixed to one another or to other structures
- N3 Metastasis to ipsilateral internal mammary lymph node(s)

Distant Metastasis (M)

- M0 No distant metastasis

STAGE GROUPING

Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1, N2	M0
Stage IIIB	T4	Any N	M0
	Any T	N3	M0

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each patient, this section must be photocopied, completed and submitted to the Data Operations Center in Seattle (see Section 14.4).

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

- ____ 5.1 Patients must be women with a histologically confirmed diagnosis of locally advanced or inflammatory (see Section 10.1a) breast carcinoma. Histologic confirmation shall be by either core needle biopsy or incisional biopsy. Punch biopsy is allowed if invasive breast cancer is documented.

Inflammatory? (circle one) YES NO

- ____ 5.2 Patients must meet one of the criteria defined below (indicate one):
- ____ a. Selected Stage IIB (T3, N0, M0) or IIIA (T3, N1-2, M0 or T0-2, N2, M0) disease judged primarily unresectable by an experienced breast surgeon; or otherwise deemed appropriate candidates for neoadjuvant treatment.
 - ____ b. Stage IIIB (T4, Any N, M0) or (Any T, N3, M0) disease.
- ____ 5.3 Patients must not have any distant metastases.
- ____ 5.4 Patients must not have received any prior chemotherapy or hormonal therapy for breast cancer.
- ____ 5.5 Patients must not have received prior radiation therapy and must not have undergone prior definitive surgery for breast cancer.
- ____ 5.6 Physical examination, chest x-ray and any x-rays or scans needed for tumor assessment must be performed within 42 days prior to registration.

Date of physical examination _____

Date of chest x-ray _____

Date of x-rays/scans for tumor assessment _____

- ____ 5.7 Patients with the clinical diagnosis of congestive heart failure or angina pectoris are NOT eligible. Patients with hypertension or age > 60 years must have a MUGA or echocardiogram scan performed within 42 days prior to registration (indicate NA if no MUGA required) and LVEF % must be greater than the institutional lower limit of normal.

Hypertension or age > 60 years? (circle one) YES NO

Date of baseline MUGA/echocardiogram _____ LVEF % _____

ILLN _____

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

- ____ 5.8 Patients must have a serum creatinine and bilirubin \leq the institutional upper limit of normal, and an SGOT or SGPT $\leq 2 \times$ the institutional upper limit of normal. These tests must have been performed within 28 days prior to registration.
- Serum creatinine _____ IULN _____ Date obtained _____
- Bilirubin _____ IULN _____ Date obtained _____
- SGOT/SGPT (circle one) _____ IULN _____ Date _____
- ____ 5.9 Patients must have an ANC of $\geq 1,500/\mu\text{l}$ and a platelet count of $\geq 100,000/\mu\text{l}$. These tests must have been performed within 28 days prior to registration.
- ANC _____ Platelets _____ Date obtained _____
- ____ 5.10 No prior malignancy is allowed except for adequately treated basal cell (or squamous cell) skin cancer, in situ cervical cancer or other cancer for which the patient has been disease-free for five years.
- ____ 5.11 Patients must have a performance status of 0 - 2 by Zubrod criteria (see Section 10.2).
- ____ 5.12 For patients who consent to the clonal hematopoiesis sample submission, a pretreatment sample of forty (40) ml of peripheral blood (four 10 ml EDTA tubes supplemented with or without 2 ml of tissue culture medium) must be submitted per Section 15.0.
- ____ 5.13 Patients known to be HIV positive are not eligible due to the fact that the compromised immune system of these patients and the possibility of early death may compromise study objectives.
- ____ 5.14 Pregnant or nursing women may not participate due to the possibility of fetal harm or of harm to nursing infants from this treatment regimen. Women of reproductive potential may not participate unless they have agreed to use an effective contraceptive method.
- 5.15 In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. If Day 28 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.
- ____ 5.16 All patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.
- ____ 5.17 At the time of patient registration, the treating institution's name and ID number must be provided to the Statistical Center in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base.
- ____ 5.18 Patients must not be planning to receive any concurrent anticancer therapy while receiving protocol treatment.
- ____ 5.19 For patients registered after January 1, 2003, the patient must have signed the revised consent form reflecting the study design change distributed in protocol Amendment #2. Not applicable if before 1/1/2003.

6.0 STRATIFICATION FACTORS

Patients will be randomly assigned to Arm 1 or Arm 2 according to a dynamic allocation scheme. Treatment arms will be balanced with respect to the following stratification factor.

Disease status: inflammatory (see Section 10.1a) vs. other.

7.0 TREATMENT PLAN

For treatment or dose modification related questions, please contact Dr. Ellis at 206/288-2048 or Dr. Livingston at 206/288-1085.

7.1 Good Medical Practice

The following pre-study tests should be obtained within 42 days prior to registration in accordance with good medical practice. Results of these tests do not determine eligibility and minor deviations would be acceptable if they do not impact on patient safety in the clinical judgement of the treating physician. The Study Coordinator must be contacted if there are significant deviations in the values of these tests.

It is recommended that the following tests be done to rule out metastatic disease:

- a. CT scan of abdomen and chest.
- b. Bone scan.

7.2 ARM 1: DOXORUBICIN AND CYCLOPHOSPHAMIDE (AC) FOLLOWED BY PACLITAXEL

This regimen consists of intravenous administration of doxorubicin (Adriamycin) followed by cyclophosphamide (Cytoxan) every 21 days for a total of five cycles, unless clinical progression is documented.

Three weeks after completion of the last dose of AC, paclitaxel will be given weekly for 12 weeks.

Patients with progressive disease at any time will be removed from protocol treatment.

AC therapy will be administered on Day 1 for five 21-day cycles followed by 12 weeks of paclitaxel therapy.

AGENT	DOSE	ROUTE	DAYS	INTERVAL
Doxorubicin*	60 mg/m ²	IV, bolus	1	every 21 days x 5 cycles
Cyclophosphamide**	600 mg/m ²	IV	1	every 21 days x 5 cycles
Paclitaxel***	80 mg/m ²	IV over 1 hour	1	weekly for 12 weeks beginning three weeks after completion of last AC dose

* Doxorubicin should be administered into a vein with secure IV access.

** Rounded to the nearest 25 mg dose. All patients should be instructed on the importance of vigorous hydration during cyclophosphamide therapy.

*** Patients should be premedicated with 10 - 20 mg IV dexamethasone, 50 mg IV diphenhydramine (or equivalent), and either 300 mg IV cimetidine, 150 mg PO ranitidine or 50 mg IV ranitidine 30 - 60 minutes prior to paclitaxel infusion (or equivalent). The investigator may increase the dexamethasone if a patient experiences a hypersensitivity reaction to paclitaxel.

7.3 ARM 2: WEEKLY DOXORUBICIN WITH DAILY ORAL CYCLOPHOSPHAMIDE AND G-CSF (AC+G) FOLLOWED BY PACLITAXEL

The weekly AC + G regimen consists of weekly intravenous administration of doxorubicin (Adriamycin) and daily oral administration of cyclophosphamide (Cytoxan). Subcutaneous filgrastim (G-CSF) is administered every day, **except the day of intravenous chemotherapy administration.**

After the last dose of cyclophosphamide, paclitaxel will be given weekly for 12 weeks.

To order filgrastim (G-CSF) for patients on Arm 2 of this study, please refer to the ordering instructions in Section 3.3c and the drug order form in Section 19.2.

AC + G therapy will be administered for 15 weekly courses followed by 12 weeks of paclitaxel therapy. G-CSF will be administered for 16 weeks.

AGENT	DOSE	ROUTE	DAYS	INTERVAL
Doxorubicin	24 mg/m ²	IV, bolus	1	weekly x 15 weeks
Cyclophosphamide*	60 mg/m ²	PO	daily	continuous for 15 weeks
Filgrastim**	5 µg/kg	SQ	2 - 7	weekly x 16 weeks
Prophylactic Trimethoprim Sulfa***	1 double-strength tablet bid	PO	4 and 5	weekly x 15 weeks
Paclitaxel ****	80 mg/m ²	IV over 1 hour	1 1 hour	weekly x 12 weeks beginning after the last dose of cyclophosphamide

- * Rounded to the nearest 25 mg dose. All patients should be instructed on the importance of vigorous hydration (drinking 8 - 10 glasses of water daily) during cyclophosphamide therapy.
- ** Begin 24 hours after the administration of doxorubicin. For Week 16, filgrastim is to begin 24 hours after the first dose of paclitaxel.
- *** For patients who are unable to tolerate trimethoprim sulfa, it is suggested that they receive the alternative PCC prophylaxis dapsone 100 mg by mouth weekly. Alternatively, oral trimethoprim/sulfamethoxazole desensitization may be administered at the discretion of the treating physician (see Appendix 19.4).
- **** Patients should be premedicated with 10 - 20 mg IV dexamethasone, 50 mg IV diphenhydramine (or equivalent), and either 300 mg IV cimetidine, 150 mg PO ranitidine or 50 mg IV ranitidine 30 - 60 minutes prior to paclitaxel infusion (or equivalent). The investigator may increase the dexamethasone if a patient experiences a hypersensitivity reaction to paclitaxel.

7.4 ARMS 1 and 2: RESPONSE ASSESSMENT

Patients will have the primary disease site evaluated at least every 3 weeks with at minimum a physical examination documentation and any clinically indicated x-rays and scans for tumor measurement (see Sections 9.1 and 9.2).

7.5 ARMS 1 and 2: SURGERY

Post-chemotherapy surgery for patients with a response or stable disease must take place no sooner than 21 days following the completion of IV chemotherapy to allow for normalization of blood counts. Unless there are exceptional circumstances, surgery should be modified radical mastectomy (mastectomy with axillary node dissection). For patients with excellent clinical response who decline modified radical mastectomy, minimal surgical resection should include lumpectomy with clear surgical margins and axillary dissection. Surgery should take place within 6 weeks after completion of chemotherapy unless complications require a delay.

Patients who progress at any time will be removed from protocol treatment. Further treatment (radiation or additional chemotherapy) is allowed and will be per the treating physician's discretion. Any additional treatment must be documented on the Follow-Up Form (Form #61519). (See Appendix 19.6.)

NOTE: For patients who consent to the clonal hematopoiesis sample submission, pre-surgical blood samples are to be submitted per Sections 14.9 and 15.0.

7.6 Criteria for Removal from Protocol Treatment:

- a. Progression of disease (as defined in Section 10.3).
- b. Delay of treatment for more than 3 weeks for hematologic toxicity or more than 2 weeks for other toxicity.
- c. Unacceptable toxicity.

- d. Completion of planned treatment.
 - e. The patient may withdraw from the study at any time for any reason.
- 7.7 All reasons for discontinuation of treatment must be documented clearly on the Off-Treatment Notice (Form #61571).
- 7.8 All patients will be followed for five years or until death, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 This study will utilize the CTC (NCI Common Toxicity Criteria) Version 2.0 for toxicity and Adverse Event reporting. A copy of the CTC Version 2.0 can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). **All appropriate treatment areas should have access to a copy of the CTC Version 2.0.**

8.2 **Toxicities and Dose Modifications for ARM 1: doxorubicin and cyclophosphamide (AC)**

Chemotherapy delays and dose modifications for hematologic toxicity are based on counts from Day 1 of the cycle.

Dose reduction of either doxorubicin or cyclophosphamide is not allowed, except as noted below.

If a patient develops multiple toxicities included in the list below, delay treatment or modify dose based on the greatest toxicity. Dose re-escalations are not allowed after dose reductions unless otherwise specified.

NOTE: If G-CSF administration is deemed necessary for patients on Arm 1, the drug should be obtained from commercial sources. G-CSF is not being provided for patients treated on Arm 1 of this study.

a. HEMATOLOGIC TOXICITIES - ARM 1 (AC)

Toxicity	Treatment Modification
ANC < 1,500/mm ³	<p>Hold both doxorubicin and cyclophosphamide until ANC ≥ 1,500. Repeat counts at least weekly. Resume at full dose with G-CSF support when counts have recovered. G-CSF should begin on Day 2 at 5 µg/kg/day and continue for 10 days. G-CSF should be discontinued at least 24 hours prior to the next cycle of chemotherapy. All remaining cycles of AC will be given with G-CSF support. If, despite G-CSF support, ANC < 1,500 on Day 1 of subsequent cycles, do the following:</p> <p>IF ANC recovers to ≥ 1,500 in ≤ 1 week, give AC at full dose.</p> <p>IF ANC recovers to ≥ 1,200 in 2 - 3 weeks, give AC as follows:</p> <p style="padding-left: 20px;">Doxorubicin 50 mg/m² Cyclophosphamide 500 mg/m²</p> <p>IF ANC < 1,200 after the 3-week delay, remove patient from protocol treatment.</p>
Platelets < 100,000	<p>Hold both doxorubicin and cyclophosphamide until platelets are ≥ 100,000. Resume at full dose. If platelet count fails to recover to ≥ 100,000 within 3 weeks, remove the patient from protocol treatment.</p>
Febrile Neutropenia* Grade 3	<p>Give all remaining cycles with G-CSF support. If a second episode occurs, all remaining cycles will be given with G-CSF support and ciprofloxacin (500 mg po, bid) or antibiotic of choice. If a third episode occurs, the remaining cycles of AC will be reduced by 25% (based on the current dose) when chemotherapy is resumed. If a fourth episode occurs, remove the patient from protocol treatment.</p>

*Febrile neutropenia is defined as a fever ≥ 38.5°C in the presence of neutropenia (ANC < 1,000).

b. OTHER TOXICITIES - ARM 1 (AC)

TOXICITY	TREATMENT MODIFICATION
Infection \geq Grade 3	Give all remaining cycles with G-CSF support and ciprofloxacin (500 mg po, bid) or antibiotic of choice. If a <u>second episode</u> of Grade 3 or 4 infection occurs, the remaining cycles of AC will be reduced by 25% (based on current dose) when chemotherapy is resumed.
Gastrointestinal Grade \geq 3	If full doses cannot be administered, hold both doxorubicin and cyclophosphamide. Resume at full dose when can be tolerated. No more than a <u>two week delay</u> will be allowed for this recovery. If, after a <u>two week delay</u> , the toxicity is not resolved, remove the patient from protocol treatment.
Mucositis Grade \geq 3	Hold doxorubicin. Resume at full dose next cycle if toxicity recovers to \leq Grade 2. If patient continues to have mucositis \geq Grade 3 when next cycle is due, contact the Study Coordinator.
Liver Function Abnormalities Grade \geq 2 Bilirubin $> 1.5 \times$ IULN or SGOT/SGPT $> 2.5 \times$ IULN	Hold chemotherapy while cause is determined. If rise is not due to metastatic disease and levels return to $<$ Grade 2 within two weeks, resume at full dose. If delay is <u>longer than 2 weeks</u> , contact the Study Coordinator.
Cardiac changes** Grade \geq 3	AC therapy must be discontinued and the patient removed from protocol treatment if the patient has symptoms of CHF (e.g., dyspnea, tachycardia, cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, etc.) and a diagnosis of CHF is confirmed or if the patient has a myocardial infarction.
Hematuria (Hemorrhagic cystitis) Grade 3 or 4	Discontinue cyclophosphamide and contact the Study Coordinator.
Grade \geq 3*** Hand-foot syndrome with desquamation, vesicle formation, or pain which interferes with walking	Hold doxorubicin, cyclophosphamide and G-CSF for one week. Resume at full previous dose in one week if improved. Otherwise, reduce current dose of doxorubicin by 25%.

** The presence of PACs or PVCs without cardiac dysfunction is **not** an indication to stop doxorubicin. Acute dysrhythmias, which may occur during and shortly after doxorubicin infusion, are not an indication to stop doxorubicin.

*** Hand-foot syndrome often begins as tenderness or mild erythema at the lateral margins of the nails (usually of the hands) or as tenderness and edema over the calluses of the feet. Patients who show these early symptoms or have persistent significant involvement should do the following:

1. Take vitamin B6 (pyridoxine) 100 mg three times daily;
2. Regularly use Bag Balm or Australian tea tree lotion or oil on the hands and feet.

Please refer to Section 8.4 for paclitaxel dose modifications.

8.3 Toxicities and Dose Modifications for ARM 2: Weekly doxorubicin and daily cyclophosphamide + G-CSF (AC+G)

Chemotherapy dose modifications and delays for toxicities on the day IV therapy is due shall be based on the guidelines below.

If a patient develops multiple toxicities included in the list below, delay treatment or modify dose based on the greatest toxicity. Dose re-escalations are not allowed after dose reductions unless otherwise specified.

a. HEMATOLOGIC TOXICITIES - ARM 2 (AC+G)

TOXICITY	TREATMENT MODIFICATION
ANC \leq 1,200/mm ³	<p>Hold both doxorubicin and cyclophosphamide for one week; continue G-CSF. Then proceed as follows:</p> <p>IF ANC recovers to $> 1,200$ in ≤ 1 week, resume both doxorubicin and cyclophosphamide at full doses.</p> <p>IF ANC $< 1,200$ but $> 1,000$ hold doxorubicin and resume cyclophosphamide at full dose.</p> <p>IF ANC remains $\leq 1,000$ for another week, reduce current dose of AC as follows when therapy resumes:</p> <p>Doxorubicin 18 mg/m² IV Day 1 Cyclophosphamide 45 mg/m² PO qd.</p> <p>IF ANC fails to recover to $> 1,000$ by week 3, remove the patient from protocol treatment.</p>
Platelets $< 100,000/\text{mm}^3$	<p>Hold both doxorubicin and cyclophosphamide, but continue G-CSF. Hold until platelets are $\geq 100,000$. Resume at full dose. If platelet count fails to recover to $\geq 100,000$ within 3 weeks, remove the patient from protocol treatment.</p>
Febrile Neutropenia* Grade 3	<p>Give all remaining cycles with ciprofloxacin (500 mg po, bid) or antibiotic of choice. If a second episode occurs, the remaining cycles of AC will be reduced by 25% (based on current dose) when chemotherapy is resumed. If a third episode occurs, remove patient from protocol treatment.</p>

*Febrile neutropenia is defined as a fever $\geq 38.5^\circ \text{C}$ in the presence of neutropenia (ANC $< 1,000$).

b. OTHER TOXICITIES - ARM 2 (AC+G)

TOXICITY	TREATMENT MODIFICATION
Infection \geq Grade 3	Give all remaining cycles with ciprofloxacin (500 mg po, bid) or antibiotic of choice. If a <u>second episode</u> of Grade 3 or 4 infection occurs, the remaining cycles of AC will be reduced by 25% (based on current dose) when chemotherapy is resumed.
Gastrointestinal Grade \geq 3	If full doses cannot be administered, hold both doxorubicin and cyclophosphamide. Resume at full dose when can be tolerated. No more than a two week delay will be allowed for this recovery. If, after a two week delay, the toxicity is not resolved, remove the patient from protocol treatment.
Mucositis Grade \geq 3	Hold doxorubicin; hold cyclophosphamide only if patient is unable to take oral medication. Resume at full dose the next week if mucositis \leq Grade 2. If patient continues to have mucositis \geq Grade 3 the next week, call the Study Coordinator.
Liver Function Abnormalities Grade \geq 2 Bilirubin $>$ 1.5 x IULN or SGOT/SGPT $>$ 2.5 x IULN	Hold chemotherapy while cause is determined. If rise is not due to metastatic disease and levels return to < Grade 2 within two weeks , resume at full dose. If delay is <u>longer than 2 weeks</u> , contact the Study Coordinator.
Cardiac changes** Grade \geq 3	AC therapy must be discontinued and the patient removed from protocol treatment if the patient has symptoms of CHF (e.g. dyspnea, tachycardia, cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, etc.) and a diagnosis of CHF is confirmed or if the patient has a myocardial infarction.
Hematuria (Hemorrhagic cystitis) Grade \geq 3 Grade \geq 3 Hand-foot syndrome with desquamation, vesicle formation or pain which interferes with walking***	Discontinue cyclophosphamide and contact the Study Coordinator. Hold doxorubicin, cyclophosphamide and G-CSF for one week. Resume at full dose in <u>one week</u> if improved. Otherwise, reduce dose of doxorubicin by 25% (based on current dose).

** The presence of PACs or PVCs without cardiac dysfunction is **not** an indication to stop doxorubicin. Acute dysrhythmias, which may occur during and shortly after doxorubicin infusion, are not an indication to stop doxorubicin.

*** Hand-foot syndrome often begins as tenderness or mild erythema at the lateral margins of the nails (usually of the hands) or as tenderness and edema over the calluses of the feet. Patients who show these early symptoms or have persistent significant involvement should:

1. Take vitamin B6 (pyridoxine) 100 mg three times daily;
 2. Regularly use Bag Balm or Australian tea tree lotion or oil on the hands and feet.
- c. A 25% dose reduction in G-CSF may be instituted for the following conditions:
- ANC > 20K on a treatment day or
 - ANC > 10K and the patient is experiencing significant bone aches

This reduction can be achieved by:

- Decreasing the individual doses of G-CSF by 25% up to two such 25% reductions can be made during the study (from 400 μ g to 300 μ g, then if necessary, from 300 μ g to 225 μ g)
- Decreasing the days of the week that G-CSF is given, but to no less than 5 days of injections.

If problems persist please contact the study coordinator (see Section 8.5).

Please refer to Section 8.4 for paclitaxel dose modifications.

8.4 Dose Modifications for Paclitaxel - Arms 1 and 2

- a. Hematologic: If ANC < 1,500 or platelets < 75,000, therapy will be withheld until ANC \geq 1,500 or platelets \geq 75,000. Patients with previous ANC < 1,500 will resume paclitaxel therapy at a dose reduced by 25% for all subsequent cycles.
- b. Hepatic: Patients with Grade 4 hepatic toxicity will have paclitaxel treatment held until toxicity recovers to \leq Grade 3.
- c. Stomatitis:

If Grade 3/4 stomatitis occurs, hold paclitaxel until recovery to Grade \leq 1, and then resume at a 25% dose reduction for this and subsequent cycles.

d. Paclitaxel hypersensitivity reactions:

Treatment shall be discontinued for Grade 4 paclitaxel hypersensitivity reactions. There are no dose reductions for hypersensitivity reactions.

Hypersensitivity	Treatment Guidelines
Grade 1	<ul style="list-style-type: none">Consider decreasing the rate of infusion until recovery from symptoms; closely monitor patient.Resume paclitaxel infusion at the planned initial rate after symptoms resolve on that day of treatment.
Grade 2	<ul style="list-style-type: none">Interrupt paclitaxel infusion immediately.Give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV; monitor patient until symptoms resolve.Resume paclitaxel infusion after recovery of symptoms; depending on the physician's assessment of the patient, infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate.Depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the next cycle of treatment, and the rate of infusion should be decreased initially and then increased back to the recommended 1-hour
Grade 3	<ul style="list-style-type: none">Immediately discontinue paclitaxel infusion.Give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV and/or epinephrine as needed; monitor patient until resolution of symptoms.Resume paclitaxel infusion after recovery of symptoms on that day of treatment; depending on the physician's assessment of the patient, infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate.Depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the next cycle of treatment, and the rate of infusion should be decreased initially and then increased back to the recommended 1-hour
Grade 4	<ul style="list-style-type: none">NO FURTHER PACLITAXEL THERAPY.

e. Peripheral neuropathy:

Patients who experience \geq Grade 3 peripheral neuropathy should have their dose held for one week. If the peripheral neuropathy has improved by the next week, resume at full dose. If the peripheral neuropathy is not improved, hold dose another week then resume with a reduction of 10 mg/m² for this and subsequent cycles.

f. Other:

If toxicities are \leq Grade 2, manage symptomatically, if possible, and treat without dose reduction. If toxicities are $>$ Grade 2, treatment should be withheld (except for anemia) until recovery to \leq Grade 1 (or baseline, if baseline was $>$ Grade 1).

- 8.5 For treatment or dose modification related questions, please contact Dr. Ellis at 206/288-2048 or Dr. Livingston at 206/288-1085.
- 8.6 Unexpected or fatal toxicities (including suspected reactions) must be reported to the Operations Office, to the Study Coordinator, to the IRB and the NCI. The procedure for reporting adverse reactions is outlined in Section 16.0.

9.0 STUDY CALENDAR S0012, "A Comparative Randomized Study of Standard Doxorubicin and Cyclophosphamide Followed by Weekly Paclitaxel vs. Weekly Doxorubicin and Daily Oral Cyclophosphamide Plus G-CSF Followed by Weekly Paclitaxel as Neoadjuvant Therapy for Inflammatory and Locally Advanced Breast Cancer"

9.1 S0012, ARM 1: Doxorubicin and Cyclophosphamide (AC) Followed by Paclitaxel

REQUIRED STUDIES	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Ω	Q	§
	PRE STUDY	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15	Follow-Up	
PHYSICAL																		
History & Physical Exam \ddagger	X																	
Weight & Performance Status	X																	
Disease Assessment π	X																	
Toxicity Notation	X																	
LABORATORY																		
CBC, Platelets & Differential	X																X	
Serum Creatinine	X																X	
Bilirubin	X																X	
SGOT or SGPT	X																X	
Blood samples for clonal hematopoiesis \natural	X																X	
X-RAYS AND SCANS																		
Chest x-ray	X																X	
MUGA or Echocardiogram	X*																	
X-rays/scans for disease assessment \mathfrak{f}	X																	
CT of chest/abdomen	XØ																	
Bone scan	XØ																	
TREATMENT (See Section 7.0)																		
Doxorubicin β	XØ																	
Cyclophosphamide β	XØ																	
Paclitaxel \dagger	XØ																	
Post Chemotherapy Surgery																		

NOTE: Data submission forms are found in Section 18.0. Forms submission guidelines may be found in Section 14.0.

π A detailed description of the primary tumor, including results of physical exam or results of imaging studies, must be provided.

\natural These tests are recommended presudy for good medical practice.

* MUGA or echocardiogram will be obtained presudy for patients with hypertension or age > 60 years.

β Doxorubicin and cyclophosphamide are administered on Day 1 of each cycle.

Ø Definitive surgery for patients with response or stable disease must take place no sooner than 21 days following the end of the chemotherapy to allow for normalization of blood counts and within 6 weeks after the completion of chemotherapy unless complications require a delay.

§ Adjuvant treatment after post-chemotherapy surgery is at the physician's discretion. Post-surgery therapy must be documented on the Follow-Up Form (Form #61519). (See Appendix 19.6).

† After off treatment, follow-up assessments will be done every 6 months for one year. After one year, patients will be followed with physical exam and submission of the Southwest Oncology Group Follow-Up Form (Form #61519) annually for 4 more years. Any occurrences of leukemia or MDS must be recorded.

‡ History and physical exam will be performed every 3 weeks while on protocol treatment.

£ X-rays/scans for disease assessment should be done every 3 weeks or as clinically indicated and the same methods used at baseline should be used throughout.

¶ For patients who consent to the clonal hematopoiesis sample submission, see Section 15.0.
 || For patients who consent to the clonal hematopoiesis sample submission, see Section 15.0.
 † Paclitaxel will be given weekly for 12 weeks beginning 3 weeks after the completion of last dose of AC.

9.0 STUDY CALENDAR S0012, "A Comparative Randomized Study of Standard Doxorubicin and Cyclophosphamide Followed by Weekly Paclitaxel vs. Weekly Doxorubicin and Daily Oral Cyclophosphamide Plus G-CSF Followed by Weekly Paclitaxel as Neoadjuvant Therapy for Inflammatory and Locally Advanced Breast Cancer"

9.2 S0012, ARM 2: Doxorubicin and Cyclophosphamide + G-CSF(AC+G) Followed by Paclitaxel

REQUIRED STUDIES	WEEK 1												WEEK 2												WEEK 3							F	Ω	§	√
	PRE STUDY	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28						
PHYSICAL																																			
History & Physical Exam [¥]	X																														X				
Weight & Performance Status	X																														X				
Disease Assessment ^f	X																														X				
Toxicity Notation	X																														X				
LABORATORY																																			
CBC, Platelets & Differential	X																														X				
Serum Creatinine	X																														X				
Bilirubin	X																														X				
SGOT or SGPT	X																														X				
Blood samples for clonal hematopoiesis [¶]	X																														X				
X-RAYS AND SCANS																																			
Chest x-ray	X																																		
MUGA or Echocardiogram	X*																																		
X-rays/scans for disease assessment [#]	X																																		
CT of chest/abdomen	XO																																		
Bone scan	XO																																		
TREATMENT (See Section 7.0)																																			
Doxorubicin	X																																		
Cyclophosphamide	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Trimethoprim sulfam B	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Filgrastim (G-CSF)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Paclitaxel [†]																																			
Post-Chemotherapy Surgery																															X				

NOTE: Data submission forms are found in Section 18.0. Forms submission guidelines may be found in Section 14.0.

¶ These tests are recommended prestudy for good medical practice.
f Disease should be assessed at least every 3 weeks during treatment. A detailed description of the primary tumor, including results of physical exam or results of imaging studies, must be provided.

* MUGA or echocardiogram will be obtained prestudy for patients with hypertension or age > 60 years.

Omit if the patient is allergic to sulfa drugs.

† Definitive surgery for patients with response or stable disease must take place no sooner than 21 days following the end of the chemotherapy to allow for normalization of blood counts and within 6 weeks after the completion of chemotherapy unless complications require a delay.

‡ Weekly cycles of AC+G therapy will repeat as specified for 15 Weeks.
§ Adjuvant treatment after post-chemotherapy surgery is at the physician's discretion. Post-surgery therapy must be documented on the Follow-Up Form (Form #61519).
(See Appendix 19.6)

√ After off treatment, follow-up assessments will be done every 6 months for one year. After one year, patients will be followed with physical exam and submission of the Southwest Oncology Group Follow-Up Form (Form #61519) annually for 4 more years. Any occurrences of leukemia or MDS must be recorded.

¥ History and physical exam performed every 3 weeks while on treatment.

≠ X-rays/scans for disease assessment should be done every 3 weeks or as clinically indicated and the same methods used at baseline should be used throughout.

¶ For patients who consent to the clonal Hematopoiesis sample submission, see Section 15.0.

○ Treatment with filgrastim will continue one week after completion of AC therapy for a total of 16 weeks (see Section 7.3).

† Paclitaxel will be given weekly for 12 weeks beginning after the last dose of cyclophosphamide.

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10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Definitions

- a. **Inflammatory Disease:** Erythema AND peau d'orange involving half or more of the breast with a histologic diagnosis of breast cancer. The findings of focal dermal lymphatic involvement on histology does not constitute inflammatory breast cancer.
- b. **Microscopic path CR (pCR):** No evidence of microscopic invasive tumor at the primary tumor site in the surgical specimen.
- c. **Clinical CR:** Normal breast on physical exam. No mass, no thickening, no erythema, no peau d'orange.

10.2 Performance Status: Patients will be graded according to the Zubrod performance status scale.

<u>POINT</u>	<u>DESCRIPTION</u>
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.3 Time to Progression: From date of registration to date of first documentation of progressive disease defined as: clear increase in disease sites present at registration, or development of new sites of disease.

11.0 STATISTICAL CONSIDERATIONS

One hundred seventy five patients per arm will be required for a two-sided .05 level test of equality of probabilities to have power .9 to detect a difference of .15 between the arms (assuming the probability of pCR is approximately .15 on the standard arm).

Patients who fail treatment before surgery will be assumed not to have a pCR. Treatment failure before surgery includes death, progression or start of non-protocol treatment after early discontinuation of protocol treatment.

One interim analysis will be performed after pCR is determined on the first 175 patients. If the arms are significantly different at the .01 level, or the alternative of a .15 improvement due to Arm 2 is ruled out at the .01 level, consideration will be given to stopping the trial. The final analysis will be done at the .045 level to adjust for the early test.

Samples for clonal hematopoiesis determination will be made for one hundred patients on each arm of the S0012 study. The length of accrual is anticipated to be three years. Compliance with the blood draw at the time of surgery should be nearly complete; at 12 months following completion of treatment, approximately 15% might be anticipated to have relapsed or refused and not have samples available. The probability of clonal hematopoiesis at a particular time point can be established to within \pm 0.1 with a sample size of 100 per arm, and to within \pm 0.11 with a sample size of 85. Change in status between pretreatment, at the time of surgery and six and twelve months post-surgery samples will be explored, as will concordance of the HUMARA and microsatellite assays. Association of treatment, pre-study, patient characteristics, and tumor-related variables with presence or absence of clonality by HUMARA or microsatellite assays will also be explored. For example, a two-sided .05 level test of the association of the treatment group with presence or absence of clonality will have adequate power to detect differences of .25 or greater (power at least .93 for the pretreatment and three month time point and .88 for the 12 month post-treatment time point, if sample size decreased to 85 per arm).

The study will be monitored by the Southwest Oncology Group Data and Safety Monitoring Committee according to NCI guidelines and Southwest Oncology Group policy.

If the 9/23/02 amendment results in increased accrual to S9625 levels, accrual should be complete in approximately 3.5 years.

12.0 DISCIPLINE REVIEW

There will be no discipline review for this study.

13.0 REGISTRATION GUIDELINES

- 13.1 Patients must be registered prior to initiation of treatment (no more than five working days prior to planned start of treatment).
- 13.2 For either method of registration, the individual registering the patient must have completed the appropriate Southwest Oncology Group Registration Form. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

The individual registering the patient must also be prepared to provide the treating institution's name and ID number in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base. Patients will not be registered if the IRB approval date has not been provided or is > 365 days prior to the date of registration.

13.3 Registration procedures

- a. Patients from member, CCOP or approved affiliate institutions may be registered via the Web Reg program (<http://www.swogstat.org/webapps/secured/logon.asp>) at any time except maintenance down times (the logon page shows down times). Institutions with internet access are encouraged to register this way. For first time users, a "Starter Kit" can be accessed at:

<https://www.swogstat.org/webapps/secured/starterkit.htm>

The person registering the patient must be in the Southwest Oncology Group Roster. Call the Operations Office (210/677-8808) if an addition to the roster is necessary. A valid password allowing Web registration is also necessary. Each institution has a Web Registration Administrator (listed on the "Starter Kit" site) who may add Web Reg users at their institution and assign passwords to new users. Any Web Reg user can change their own password using the Administrator program (as explained in the Starter Kit). For other password problems or problems with the Web Reg program, email webreghelp@crab.org.

- b. If the Web Reg program is not used, the registration must be done by phone.

Member, Affiliate and CCOP Institutions

Registration by phone of patients from member, affiliate and CCOP institutions must be done through the Southwest Oncology Group Data Operations Center in Seattle by telephoning 206/652-2267, 6:30 a.m. to 4:00 p.m. Pacific Time, Monday through Friday, excluding holidays.

13.4 For either method of registration, exceptions to Southwest Oncology Group registration policies will not be permitted.

- a. Patients must meet all eligibility requirements.
- b. Institutions must be identified as approved for registration.
- c. Registrations may not be cancelled.
- d. Late registrations (after initiation of treatment) will not be accepted.

13.5 CTSU Investigators:

Prior to the recruitment of a patient for this study, investigators and their institutions must be registered with the CTSU. Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit all IRB/regulatory documents to the CTSU before they can enroll patients. All forms and documents associated with this study can be downloaded from the **S0012** webpage on the CTSU member website (<http://members.ctsu.org>). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and all pertinent forms and documents are approved and on file with the CTSU.

In addition, all enrolling investigators must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member Web site or by calling the PMB at 301/496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Requirements for S0012 site registration:

- CTSU IRB Certification
- IRB/Regulatory Approval Transmittal Form
- IRB-approved consent form
- Personnel contact list for protocol

Patients will not be registered if the IRB approval date has not been provided or is > 365 days prior to the date of registration.

Requirements for patient enrollment on S0012:

- Patient must meet all inclusion criteria and no exclusion criteria should apply.
- Patient signed and dated consent.
- All baseline laboratory tests and prestudy evaluations performed.
- For patients who consent to the clonal hematopoiesis sample submission, a pretreatment Blood sample must be submitted per Section 15.0.

Patients must be registered prior to initiation of treatment (no more than one working day prior to planned start of treatment).

CTSU Procedures for Patient Enrollment: Contact the CTSU Patient Registration Office by calling 1-888-462-3009 to alert the CTSU Patient Registrar that an enrollment is forthcoming. Complete the following forms:

- CTSU Patient Enrollment Transmittal Form
- S0012 Eligibility Criteria (Section 5.0)
- S0012 Registration Form (Complete all sections of form except for 'Tx Assignment', and any Southwest Oncology Group-specific data fields.)

Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 8:00 a.m. and 4:30 p.m. Eastern time, Monday-Friday. The CTSU registrar will verify that the investigator is CTSU-credentialed, that enrollment forms are complete, and that all regulatory and patient eligibility requirements have been met. The CTSU registrar will follow-up with the CTSU investigative site to resolve any discrepancies. Once investigator and patient eligibility are confirmed, the CTSU registrar will contact SWOG to obtain a treatment assignment and assignment of a unique patient ID. The CTSU registrar will then contact the enrolling site and convey the patient ID number (to be used on all future forms and correspondence) and the patient's treatment assignment. This will be confirmed by an e-mail or fax to the enrolling site.

14.0 DATA SUBMISSION SCHEDULE

- 14.1 Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients with inadequate documentation to determine eligibility will be deemed ineligible.
- 14.2 Copies of all forms used for this study are included in the Master Forms Set in Section 18.0. With the exception of the model consent form and the S0012 Registration Form, these forms should be photocopied, completed, and submitted for all patients.
- 14.3 Group Member Institutions and CCOP Institutions must submit one copy of all data forms directly to the Southwest Oncology Group Data Operations Center in Seattle at the address below. Affiliates must submit (number of copies to be determined by the Group member) copies of all forms to their Group member institution for forwarding to the Southwest Oncology Group Data Operations Center in Seattle at the following address:

Southwest Oncology Group Data Operations Center
Cancer Research And Biostatistics
1730 Minor Ave, STE 1900
Seattle, WA 98101-1468

OR, Member and CCOP institutions may submit data via facsimile to 206/652-4612. Faxed data must be accompanied by the Data Submission Facsimile Cover Sheet.

14.4 CTSU INVESTIGATORS

All data forms for this study are available for download from the CTSU member website at <http://members.ctsu.org>. CTSU investigators should use the protocol-specific SWOG forms, adhere to the SWOG schedule for data submission, and forward all forms and reports to the CTSU Data Operations Center in the following manner:

- Patient entry forms and adverse event forms should be faxed to the CTSU according to instructions in the CTSU patient registration procedures and adverse event reporting sections of the protocol.

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- All other original forms and reports must be *mailed* directly to the CTSU Data Center accompanied by a completed CTSU Data Transmittal Form; the CTSU will then forward all information to the Southwest Oncology Group.
- Transmittals and reports associated with blood specimen submission should be sent to the address listed in Section 15.3 of the protocol. Do not send specimens or original forms to CTSU. Copy the CTSU on transmittals only (i.e., Specimen Submission Form (Form #1951). Upon receipt, send the CTSU a copy of the final report.

CTSU REPORT FORMS AND DATA MUST BE SENT TO:

Westat
CTSU Data Operations Center
1441 W. Montgomery Avenue
Rockville, MD 20850-2062

Phone: 1-888-823-5923
Fax: 1-888-691-8039

A CTSU DATA TRANSMITTAL SHOULD ACCOMPANY ALL FORMS AND REPORTS SUBMITTED TO CTSU.

14.5 FOR PATIENTS WHO CONSENT TO THE CLONAL HEMATOPOIESIS SAMPLE SUBMISSION: AT THE TIME OF REGISTRATION:

Submit pre-study blood sample to the City of Hope National Medical Center per Section 15.0 (also see Section 5.12).

A copy of the Specimen Submission Form (Form #1951) should be submitted along with each sample and a copy should also be submitted to the Southwest Oncology Group Statistical Center.

14.6 WITHIN 14 DAYS OF REGISTRATION:

Submit copies of the following:

- a. **S0012** Breast Cancer Prestudy Form (Form #34877)
- b. A completed copy of Section 5.0 of the protocol documenting history and physical and prestudy tests/exam results
- c. Initial Pathology Report

14.7 AT 6 WEEKS AND 12 WEEKS DURING AC TREATMENT AND AFTER FINAL AC TOXICITY ASSESSMENT (PRIOR TO BEGINNING PACLITAXEL):

Submit copies of the **S0012** AC Assessment Form (Form #23540) documenting required parameters as specified in the Study Calendar.

14.8 WITHIN 14 DAYS OF DISCONTINUATION OF AC CHEMOTHERAPY:

Submit copies of the Off-Treatment Notice (Form #61571) and the **S0012** Dose Form for Arm 1 (Form #40274) or Arm 2 (Form #32573).

14.9 AFTER COMPLETION OF ALL CHEMOTHERAPY:

Submit copies of the **S0012** Paclitaxel Assessment Forms (Form #6444) (after completion of paclitaxel and resolution of paclitaxel related toxicities), the **S0012** Paclitaxel Dose Form - Arm 1 and Arm 2 (Form #30365) and a second Off-Treatment Notice (Form #61571).

14.10 FOR PATIENTS WHO CONSENT TO THE CLONAL HEMATOPOIESIS SAMPLE SUBMISSION: AT THE TIME OF POST-CHEMOTHERAPY SURGERY (BEFORE SURGERY):

Submit pre-surgical blood sample to the City of Hope National Medical Center per Section 15.0.

A copy of the Specimen Submission Form (Form #1951) should be submitted along with each sample and a copy should also be submitted to the Southwest Oncology Group Statistical Center.

14.11 WITHIN 14 DAYS OF POST-CHEMOTHERAPY SURGERY:

Submit copies of the Operative Report and Pathology Report.

NOTE: If post-chemotherapy surgery is not performed, document this on the Southwest Oncology Group Follow-Up Form (Form #1951) along with the reason that the surgery was not done.

14.12 AFTER OFF-TREATMENT: EVERY SIX MONTHS FOR ONE YEAR AND THEN ANNUALLY THEREAFTER FOR FOUR MORE YEARS OR UNTIL DEATH (WHICHEVER OCCURS FIRST): Post-surgery therapy must be documented on the Follow-Up Form (Form #61519). (See Appendix 19.6.)

Submit the Southwest Oncology Group Follow-Up Form (Form #61519).

14.13 FOR PATIENTS WHO CONSENT TO THE CLONAL HEMATOPOIESIS SAMPLE SUBMISSION: AT SIX AND TWELVE MONTHS AFTER POST-CHEMOTHERAPY SURGERY:

Submit six and twelve month post-surgical blood samples to the City of Hope National Medical Center per Section 15.0.

A copy of the Specimen Submission Form (Form #1951) should be submitted along with each sample and a copy should also be submitted to the Southwest Oncology Group Statistical Center.

14.14 WITHIN 14 DAYS OF PROGRESSION/RELAPSE:

Submit copies of the Southwest Oncology Group Follow-Up Form (Form #61519) documenting date, site, and method for determining progression/relapse.

14.15 WITHIN 4 WEEKS OF KNOWLEDGE OF SECOND MALIGNANCY:

Submit copies of the Southwest Oncology Group Follow-Up Form (Form #61519) documenting date, site and method for determining malignancy. (See Appendix 19.6.)

If the second malignancy is a hematologic malignancy, submit blood sample to the the City of Hope National Medical Center per Section 15.0 for clonal hematopoiesis studies. A copy of the Specimen Submission Form (Form #1951) should be submitted along with each sample and a copy should also be submitted to the Southwest Oncology Group Statistical Center.

14.16 WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit a copy of the Notice of Death (Form #61554). Also submit either a final **S0012 AC Assessment Form** (Form #23540) if death occurs while on AC treatment, or a final **S0012 Paclitaxel Assessment Form** (Form #6644) if death occurs while on paclitaxel treatment, or a Southwest Oncology Group Follow-Up Form (Form #61519) if death occurs after off treatment.

15.0 SPECIAL INSTRUCTIONS

15.1 For patients who consent to the clonal hematopoiesis sample submission: Samples will be submitted as described below:

Forty ml of peripheral blood (four 10 ml EDTA tubes supplemented with or without tissue culture medium) must be collected from each patient at each time point.

Samples will be submitted at the following time points:

- Prior to the initiation of treatment
- Just prior to surgery after the completion of neoadjuvant therapy
- At six months following surgery
- At twelve months following surgery
- In the case of diagnosis of a secondary hematologic malignancy

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15.2 Mailing Tubes for Sample Submission

Institutions may use their own EDTA (purple top) tubes.

If a delay in shipment is expected, please prepare the tubes using any standard tissue culture formation such as RPMI 1640, Alpha MEM, or McCoy's 5A, containing 10% fetal calf serum with EDTA (20 mg/ml) added as an anticoagulant.

15.3 Handling of Required Study Samples

All samples should be sent to the attention of Ms. Vicki Bedell in Dr. Marilyn Slovak's Laboratory at room temperature by overnight courier to arrive within 24 hours at the City of Hope National Medical Center.

Blood samples will each be placed in EDTA tubes supplemented with tissue culture medium and sent **the day it is obtained** by Federal Express to:

City of Hope National Medical Center
ATT: Ms. Vicki Bedell
1500 East Duarte Road
Northwest Building, Room 2265
Duarte, CA 91010
Phone: 626/359-8111 ext. 62025

Tubes should be labeled with the patient's initials, Southwest Oncology Group patient number, study number (**S0012**), and the date and time of collection. Each tube should be tightly capped and wrapped with paraffin film to prevent leakage. The tube should then be placed in a standard biohazard specimen resealable bag.

15.4 Shipping

A Specimen Submission Form (Form #1951) must be completed at the institution of origin and sent with EACH specimen, even if two samples are sent on the same day to the laboratory. The Specimen Submission Form should be placed in the pocket of the specimen bag if it has one, or in a separate resealable bag.

A copy of the Specimen Submission Form (Form #1951) with the top part filled out must also be sent to the Southwest Oncology Group Statistical Center for each sample.

The bags should be shipped in a standard styrofoam shipping container which the sites can supply. Upon receipt, specimens will be logged in the City of Hope Laboratories for the HUMARA assay. MLL gene rearrangements and the RAS gene mutation assay will be on all positive genetic instability samples.

Weekday Shipping (Arrival Monday-Friday)

PLEASE PACK TUBES CAREFULLY. Cardboard express mail envelopes alone are NOT ADEQUATE--please additionally pack the tubes in styrofoam or with extra padding. If freezing conditions or extreme heat conditions are anticipated, insulated containers are recommended. Please include the laboratory telephone number listed above on the label.

Weekend Shipping (arrival on Saturday)

Samples will be accepted on Saturdays and holidays; however, the laboratory MUST be contacted (626/359-8111 ext 62025) one or two days before the sample is shipped so that special mailing instructions for weekend specimens can be obtained. Make sure to indicate Saturday delivery on the overnight mailing label.

15.5 The Federal guidelines for shipment are as follows:

- a. The specimen must be wrapped in an absorbable material;
- b. The specimen must then be placed in an AIRTIGHT container (like a resealable bag);
- c. Pack the resealable bag and specimen in a styrofoam shipping container;
- d. Pack the styrofoam shipping container in a cardboard box.
- e. The cardboard box must be marked as "BIOHAZARD".

15.6 CTSU INVESTIGATORS

Sample submission: [For patients who consent to the clonal hematopoiesis sample submission.] Obtain, submit, and ship blood samples as instructed in Section 15.0. Do not ship specimens to the CTSU. Please provide the CTSU with a copy of the Specimen Submission Form (Form #1951).

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

For each investigational drug supplied for a study, drug disposition (drug receipt, dispensing, transfer or return) shall be maintained on the NCI Investigational Drug Accountability Record. Drug supplies must be kept in a secure, limited access storage area under the recommended storage conditions. During the course of the study, the following information must be noted on the Drug Accountability Record; the SWOG ID # and initials of the subject to whom drug is dispensed, the dose, the date(s) and quantity of drug dispensed to the subject, the date(s) and quantity of drug returned to the NCI or transferred to another NCI-approved protocol, the balance forward, lot number and recorder's initials. These Drug Accountability Records must be readily available for inspection and are open to FDA or NCI inspection at any time.

Adverse Experiences

Any adverse experience which meets protocol-specified reporting guidelines must be reported to the Operations Office Serious Adverse Events Specialist (210/677-8808), who will obtain information on the SAE. Depending on the nature of the reaction and whether it was caused by an investigational or commercial agent, the Serious Adverse Events Specialist will advise whether the report to the NCI should be phoned in, written in, or both. See guidelines below. On Phase II and III studies, all deaths considered drug-related must be reported immediately to the Serious Adverse Events Specialist. On double-blinded studies, if the investigator must know what treatment the subject received to make therapeutic decisions, the code for that particular subject can be broken by following the unblinding guidelines in the protocol.

All adverse experiences must also be reported to the Institutional Review Board within 10 days and documentation of this report sent to the Operations Office.

All adverse experiences must also be recorded in the appropriate section of the case report form. The report should include, whenever possible, the investigator's written medical judgment as to relationship of the adverse experience to study medication(s) (i.e., "probable", "possible" or "unrelated").

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 2.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

**GUIDELINES FOR REPORTING OF
ADVERSE EVENTS (AE) / ADVERSE DRUG REACTIONS (ADR)
OCCURRING WITH COMMERCIAL AGENTS**

1. WITHIN 24 HOURS OF THE EVENT CALL THE OPERATIONS OFFICE AT 210-677-8808.

2. WITHIN 10 DAYS, SEND TO THE OPERATIONS OFFICE

- a) A COPY OF THE FDA FORM 3500, including Investigator's attribution¹ of the event in item 5 (or the NCI/CTEP Secondary AML/MDS Report Form for cases of secondary AML or MDS⁵).
- b) COPIES OF PRESTUDY FORM(S), AND FLOW SHEETS FROM PRESTUDY THROUGH THE EVENT
- c) IRB NOTIFICATION DOCUMENTATION
- d) OTHER DATA AS REQUESTED DURING TELEPHONIC REPORT.

3. IN ADDITION, FOLLOW THE GUIDELINES BELOW

These guidelines apply to patients accrued to NCI research protocols which use commercial anticancer agents. The following events, when attributed as possibly, probably, or definitely related to the commercial agent(s), must be reported:

- (a) Any AE/ADR which is life threatening (Grade 4) or fatal (Grade 5) and unexpected (is not listed as a known toxicity, or is of greater severity or specificity than listed toxicity).^{2,3,4} Any occurrence of secondary AML or MDS must also be reported.⁵
- (b) Any AE/ADR which is fatal (Grade 5), even if an expected toxicity.⁴

The AE report, documented on FDA Form 3500 (or NCI/CTEP Secondary AML/MDS Report Form) should be sent within 10 days to FDA, with a copy to NCI, as indicated below:

To <u>FDA</u> :	AND	<u>NCI</u> :
Via Internet at www.fda.gov/medwatch		Mail one
or mail to MedWatch		copy to
5600 Fishers Lane		Investigational Drug Branch
Rockville, MD 20852-9787		P.O. Box 30012
or fax to 800-332-0178		Bethesda, MD 20824-0012
		or fax to 301-402-1584

Send a copy of the FDA Form 3500 or NCI/CTEP Secondary AML/MDS Report Form, plus prestudy form, flowsheets, and a copy of IRB notification to the **Operations Office** within 10 days:

Southwest Oncology Group Operations Office
ATTN: ADR Program
14980 Omicron Drive
San Antonio, TX 78245-3217

¹ Attribution: Whether the event was *definitely not, unlikely, possibly, probably, or definitely* related to protocol treatment.

² For grading reactions, see NCI Common Toxicity Criteria, Section 19.0.

³ Known toxicities are listed in the Drug Information, Background or Informed Consent Form sections of the protocol.

⁴ A report shall be submitted if the adverse event is *definitely related, probably related, or possibly related to the agent(s)*. Reactions judged definitely not treatment related should not be reported, except that all deaths while on treatment or within 30 days after treatment must be reported. Any death more than 30 days after treatment which is felt to be treatment-related must also be reported.

⁵ Secondary AML or MDS should be reported using the NCI/CTEP Secondary AML/MDS Report Form in lieu of FDA Form 3500. The Operations Office will forward this form to the Statistical Center within one working day of receipt.

Adverse Event (AE) Reporting

This study will utilize the CTC Version 2.0 for toxicity and Adverse Event (AE) reporting. A link to the CTC guidelines is available on the CTSU registered member Web site. CTSU investigators should employ definitions of adverse events as described in the protocol (see Section 16.0). All reporting should be conducted within the time frames specified in the protocol. Reports and supporting documentation must be submitted as outlined below.

Your local Investigational Review Board must be informed of all reportable serious adverse reactions.

All hard copy adverse event reports submitted to the CTSU should be accompanied by a completed CTSU Data Transmittal Form.

Treatment Arms Containing Commercial Agents Only:

Within 24 hours of the event call the operations office at 210-677-8808.

Expedited reports, copies of prestudy form(s), and flow sheets from prestudy through the event, and IRB notification documentation, are to be submitted to the CTSU (fax: 1-888-691-8039) within 10 working days of the event using form FDA Form #3500 (Medwatch).

Refer to guidelines in Section 16.0 of the protocol and submit reports to FDA, NCI, and CTSU. The CTSU will forward all forms to the Southwest Oncology Group.

For those adverse events requiring **24-hour phone notification**, the CTSU investigator is responsible for reporting the event within 24 hours to the following persons/agencies:

CTSU Data Center at 1-888-462-3009
SWOG Operations Office 210-677-8808
NCI Investigational Drug Branch at (301) 230-2330

This should be followed by an expedited report within 10 working days.

Secondary AML/MDS reporting:

CTSU investigators will submit the NCI Secondary AML/MDS Report Form and supporting documentation to the CTSU. Once received, the CTSU will send this information to the Southwest Oncology Group and the Southwest Oncology Group will forward it on to the NCI.

Pregnancy occurring while the patient is on protocol therapy:

If a female patient (or the sexual partner(s) of a male patient) becomes pregnant while receiving protocol therapy, the CTSU Patient Registrar should be notified immediately. The CTSU will then notify the Southwest Oncology Group.

17.0 BIBLIOGRAPHY

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18.0 MASTER FORMS SET

- 18.1 Attached are copies of all data forms which must be completed for this study. The Model Informed Consent form is also included, and must be reviewed and approved by the Institutional Review Board prior to registration and treatment of patients on this study.
- 18.2 Forms to be used for patients treated on this study include:
 - a. S0012 Registration Form (Form #13262)
 - b. S0012 Breast Cancer Prestudy Form (Form #34877)
 - c. S0012 AC Assessment Form (Form #23540)
 - d. S0012 Paclitaxel Assessment Form (Form #6644)
 - e. S0012 Dose Form - Arm 1 (Form #40274)
 - f. S0012 Dose Form - Arm 2 (Form #32573)
 - g. S0012 Paclitaxel Dose Form - Arm 1 and Arm 2 (Form #30365)
 - h. Off Treatment Notice (Form #61571)
 - i. Notice of Death (Form #61554)
 - j. Southwest Oncology Group Follow-Up Form (Form #61519)
 - k. Southwest Oncology Group Specimen Submission Form (Form #1951)

For IRB use only, not to be included in patient information.

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document which are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the Southwest Oncology Group Operations Office for approval before a patient may be registered to this study.

Readability Statistics:	Flesch Reading Ease	57.8 (targeted above 55)
	Flesch-Kincaid Grade Level	9.1 (targeted below 8.5)

S0012, "A Comparative Randomized Study of Standard Doxorubicin and Cyclophosphamide Followed by Weekly Paclitaxel vs. Weekly Doxorubicin and Daily Oral Cyclophosphamide plus G-CSF Followed by Weekly Paclitaxel as Neoadjuvant Therapy for Inflammatory and Locally Advanced Breast Cancer" (Title changed 9/23/02)

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your family and friends.

You are being asked to take part in this study because you have breast cancer that cannot be cured by surgery alone or because your doctor believes that it is best to give you chemotherapy to shrink your tumor before surgery.

(Paragraph below added 11/22/02)

NOTE: CTSU investigators must include the following text in the consent form: You will be entered onto this study as part of the Cancer Trials Support Unit (CTSU), a pilot project sponsored by the National Cancer Institute (NCI) to provide physicians and patients with greater access to NCI-sponsored Phase III clinical trials.

WHY IS THIS STUDY BEING DONE?

The main purpose of this study is to compare two different treatments (or "regimens") for breast cancer prior to surgery to see if one works better against breast cancer than the other. One treatment includes the drugs doxorubicin and cyclophosphamide given through a needle in a vein on Day 1 every 21 days, five times followed by paclitaxel treatment once every week for 12 weeks. (9/23/02) The other treatment includes the same two drugs but the doxorubicin is given through a needle in the vein once a week for 15 weeks and the cyclophosphamide is given by pill every day for 15 weeks followed by paclitaxel treatment once every week for 12 weeks. (9/23/02) The two drugs filgrastim and trimethoprim sulfa are also given with the doxorubicin/cyclophosphamide part of the second treatment regimen. (9/23/02) The other purpose of this study is to compare the type and severity of the side effects of each of these two treatment regimens.

The researchers would also like to learn whether the treatment for your breast cancer causes gene damage to your hematopoietic cells (early blood cells) which may be linked with the development of leukemia in a small

subgroup of breast cancer patients. The Department of Defense (DOD) has provided funds to find out this information. If you agree to submit blood samples for this purpose, small amounts of your blood (four 10 ml tubes) will be sent to a central laboratory where it will be tested for genetic damage. The submission of these samples will help in finding out if genetic damage is related to a second cancer. The studies done on your blood cells may lead to discoveries which help future patients with breast cancer.
(paragraph added 12/15/01)

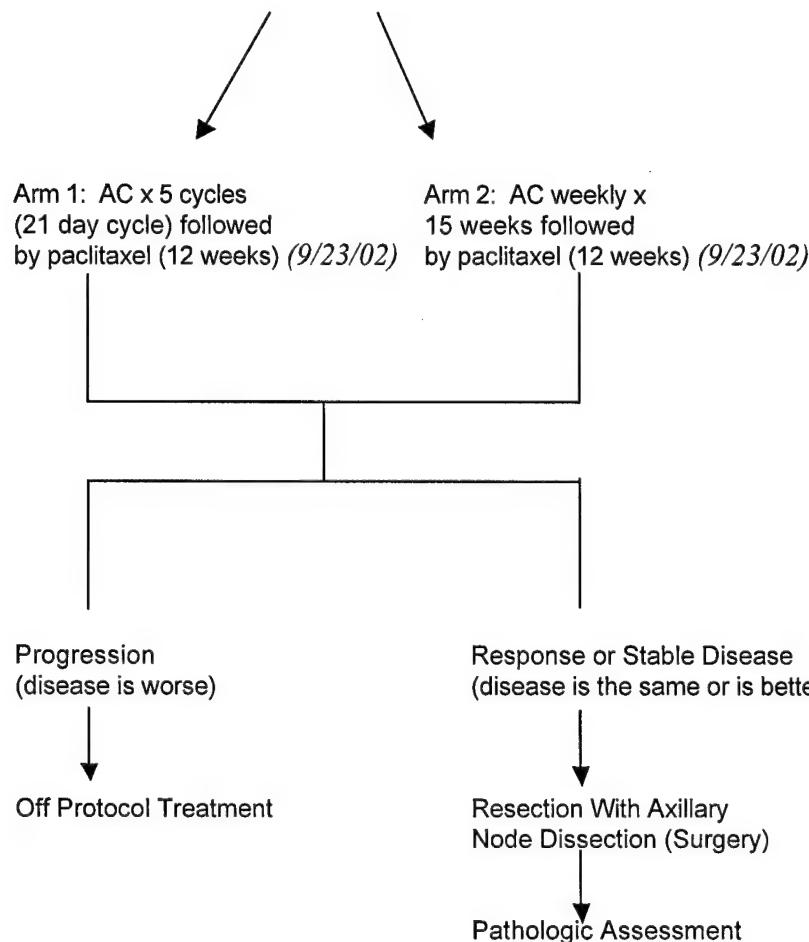
HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 350 people will take part in this study. (9/23/02)

WHAT IS INVOLVED IN THE STUDY?

SCHEMA

REGISTRATION/RANDOMIZATION



You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. Which group you are put in is done by a computer. Neither you nor the researcher will choose what group you will be in. You will have an equal chance of being placed in either group.

Regardless of which group you are assigned to, you will receive three chemotherapy drugs that are commonly used to treat breast cancer: Doxorubicin (also called Adriamycin), cyclophosphamide (also called Cytoxan) and paclitaxel (also called Taxol). (9/23/02) However, in each of these two treatment groups, Arm 1 or Arm 2 of the study, the doxorubicin and cyclophosphamide are given differently. The paclitaxel is given the same way in both groups. (9/23/02)

If you are assigned to Arm 1, you will receive the chemotherapy drugs doxorubicin and cyclophosphamide through a needle in your vein on Day 1 every 21 days for a total of five cycles (with each cycle being a 21-day timeframe). Three weeks after completing your doxorubicin/cyclophosphamide treatment, you will receive the drug paclitaxel through a needle in your vein once a week for 12 weeks. (11/22/02) *(sentence added 9/23/02)* Three to six weeks after you finish your chemotherapy treatment, you will have surgery to remove the remaining breast cancer.

If you are assigned to Arm 2, you will receive the chemotherapy drug doxorubicin through a needle in your vein once a week for 15 weeks. You will receive the chemotherapy drug cyclophosphamide by mouth (by taking a pill) every day for 15 weeks. You will also receive two additional non-chemotherapy drugs: filgrastim (also called G-CSF) and trimethoprim sulfa (also called Bactrim). Filgrastim is a "growth factor" that helps your body produce high numbers of the white blood cells that fight infection. (Chemotherapy can lower your white blood cell count and increase your chance of infection.) You will receive an injection of filgrastim every day except for the day that you receive the doxorubicin in your vein. You will receive information on the administration of filgrastim. You will also receive the drug trimethoprim sulfa by mouth by taking two pills on Days 4 and 5 of each week. Trimethoprim sulfa is an antibiotic that protects you from developing a specific type of pneumonia that is associated with the high doses of cyclophosphamide that are used in this treatment. After you finish taking cyclophosphamide, you will receive the drug paclitaxel through a needle in your vein once a week for 12 weeks. (11/22/02) *(sentence added (9/23/02))* Three to six weeks after you complete your chemotherapy treatment, you will have surgery to remove the remaining breast cancer.

The following procedures are part of regular cancer care and may be done even if you do not join the study.

- Medical history and physical exam
- Chest x-ray
- Blood tests for liver and kidney function
- Blood counts
- Other blood tests or x-rays may be done if your physician feels that they are necessary to help determine your "baseline" condition.
- If you have high blood pressure or are over 60 years of age, you will need to have a test, called a MUGA scan or echocardiogram, to determine how well your heart is working as a pump.

The following are standard procedures being done because you are in this study.

- Your weight will be measured regularly during the study: This is to make sure that the doxorubicin, cyclophosphamide, filgrastim and paclitaxel are given at the correct dose as they are all based on your weight and height.
- You will have a physical exam and possibly x-rays and scans at least once every 3 weeks while you are receiving treatment to check on your condition.

If you agree to submit samples for the clonal hematopoiesis testing funded by the Department of Defense (DOD) looking for genetic damage in blood cells, the following will be done. Blood samples (four 10 ml tubes) will be submitted before you begin treatment, just before your surgery and at 6 and 12 months after your surgery. Also, if a secondary hematologic cancer such as leukemia is diagnosed any time after you begin treatment, you are requested to submit a blood sample at that time. The blood samples can be taken from those needed for the diagnosis and treatment of your secondary cancer. If this is not possible, an additional venipuncture may be needed. The samples will be sent to the following laboratories for genetic testing. The "microsatellite instability assays" and "MLL gene rearrangement" testing will be performed at the University of Chicago, Department of Hematology/Oncology, under the direction of Dr. Wendy Stock. (1/1/04) Dr. Marilyn Slovak will direct the "HUMARA Clonality Assay" testing at the City of Hope National Medical Center in Duarte, California, Department of Cytogenetics. In the final year of the study (year three), the "RAS gene mutation analysis" will be done only for those samples that are positive for clonality. This testing (if there are any positive samples), will be done at the Fred Hutchinson Cancer Research Center in Seattle, Washington by Dr. Jerry Radich. All of these assays are described in Appendix 19.5 of the S0012 protocol. (*paragraph added 12/15/01*)

We think you will be in the study for about 27 weeks to complete your chemotherapy before surgery. (9/23/02) Your surgery is expected to take place 3 - 6 weeks after you complete your chemotherapy. After that, you will continue with regular doctor visits for checkups every 6 months for one year. After one year, you will be followed by physical exam annually for four more years. The total length of time for follow-up is five years. (7/11/03 - 2 sentences added) If you agree to submit samples for the clonal hematopoiesis testing and if you are diagnosed with a secondary hematologic malignancy at any time after you complete treatment on this study, you will see your doctor again and a blood sample will be taken at that time. (12/15/01)

The researcher may decide to take you off this study if your disease gets worse despite the treatment; the side effects of the treatment are too dangerous for you; new information about the treatment becomes available and this information suggests the treatment will be ineffective or unsafe for you. It is unlikely, but the study may be stopped early due to lack of drug supply or lack of funding.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs may be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the drug therapies are stopped, but in some cases side effects can be serious or long-lasting or permanent.

Risks and side effects related to the doxorubicin, cyclophosphamide, filgrastim and trimethoprim sulfa treatment include:

Likely:

- **Nausea and vomiting**
- **Loss of appetite**
- **Heartburn**
- **Hair loss**
- **Lowered white blood cell count, red blood cell count and platelet count leading to increased risk of infection, fatigue, or bruising or bleeding more easily**

Less Likely:

- Sores in the mouth
- Hand-foot syndrome (tingling pain and redness of the hands and feet)
- Change in color of fingernails and toenails
- Loosening of fingernails and toenails
- Inflammation or damage to the skin and around the IV tubing.
- Bladder inflammation (prevent this by drinking 8 - 10 glasses of water each day and emptying your bladder frequently)
- Pneumocystis pneumonia (for patients on Arm 2) may be caused by the lowered white blood cell counts and may be prevented by the use of an antibiotic, trimethoprim sulfa)
- Bone or joint pain (for patients on Arm 2)
- Cramps in the legs or back (for patients on Arm 2)

Less Likely but Serious:

- Heart damage
- Increased risk of leukemia

Risks and side effects related to the paclitaxel treatment schedule: (*Section added 9/23/02*)

Likely

- Lowered blood cell counts, increased chance of infection or bleeding
- Numbness or tingling in legs and arms or fingers and toes
- Muscle pain
- Joint pain
- Nausea
- Vomiting
- Hair loss

Less Likely:

- Lowered or raised blood pressure
- Slow heartbeat
- Swelling at injection site
- Diarrhea
- Mouth sores
- Weakness
- Nail changes

Less Likely: (contd.) (section added continued 9/23/02)

- Water retention
- Malaise
- Changes in taste
- Mood changes
- Trouble walking
- Blurred vision/changes in vision
- Decreased motility in colon
- Abdominal discomfort
- Inflammation of the intestine

Less Likely, but Serious:

- Hypersensitivity reaction including low blood pressure, difficulty breathing and rash
- Inflammation of the lungs
- Seizures
- Liver dysfunction
- Heart damage

Risks from venipuncture (needed for drawing blood samples for the clonal hematopoiesis testing): The risk from venipuncture is very small. There may be some bruising or bleeding at the site the blood is drawn from. (paragraph added 12/15/01)

Reproductive risks: Because the drugs in this study can affect an unborn baby, you should not become pregnant while on this study. You should not nurse your baby while on this study. Ask about counseling and more information about preventing pregnancy. Doxorubicin and cyclophosphamide may also damage your reproductive cells (eggs) and, if you are still menstruating, you may begin having irregular menstrual periods or stop menstruating altogether. This side effect may be permanent. You may not be able to have children after receiving this treatment. This is more likely if you are over the age of 40.

Very rarely, severe bleeding or infection may result from lowered blood counts, and could be fatal.

You may receive other drugs as part of your treatment (erythropoietin [also known as "epo"], antibiotics, anti-nausea drugs) that are not part of this study and may never be needed. If your doctor feels it is necessary to use any of these drugs to treat the side effects of your

chemotherapy, he/she will discuss the risks and benefits with you at that time. Other drugs not mentioned in this consent may be used to prevent or treat the side effects of chemotherapy. The risks, benefits and possible side effects of any drug prescribed will be explained to you. As with any drug, there may be unanticipated side effects.

For more information about risks and side effects, ask the researcher or contact _____.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

We cannot and do not guarantee that you will benefit if you take part in this study. The treatment you receive may even be harmful. Your doctors feel that your participation in this study will give you at least as good a chance as you might expect from other treatments. We hope the information learned from this study will benefit other patients with breast cancer in the future.

The possible benefits of taking part in the study are the same as receiving chemotherapy prior to surgery without being in the study.

There is no benefit for your taking part in the clonal hematopoiesis testing portion of this protocol. There may be some benefit to patients with breast cancer in the future. (paragraph added 12/15/01)

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, you have these options:

You may choose to participate in other studies giving neoadjuvant chemotherapy (chemotherapy before surgery) or other chemotherapy. You may choose to receive other chemotherapy combinations commonly used for this type of breast cancer, most containing the drug doxorubicin, without being in a study. You may choose treatment with other new experimental drugs.

You may also choose to have no anti-cancer treatment at this time (with care to make you feel more comfortable).

You can get treatment for breast cancer without being on this study. All of the treatment on this study may be available at this center or at other locations.

There may be other ways (besides the clonal hematopoiesis testing used in this study) of determining if there is genetic damage in your cells. The methods used in this study are comparable to others that may be available. You also have the option of not having this procedure done on your blood samples. (paragraph added 12/15/01)

Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

Data is stored in a secured and confidential computer record at the Southwest Oncology Group Statistical Center. No submitted forms, reports or internal applications include name, SSN, zip code or country and only patient initials are used. *(paragraph added 12/15/01)*

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as: the National Cancer Institute, the Food and Drug Administration, Amgen Pharmaceutical Company and the Southwest Oncology Group. Additionally, if you agree to submit samples for the clonal hematopoiesis testing, the U.S. Army Medical Research and Material Command may inspect your research records. *(12/15/01)*

If we publish the information we learn from this study in a medical journal, you will not be identified by name or in any other way.

It is suggested that CTSU institutions incorporate the following paragraph in their consent forms. *(12/15/01)* While you are participating in this study a record of your progress on this study will be kept in a confidential form at [INSERT NAME OF INSTITUTION] and sent to the sponsor who will add this information to a computer file. The confidentiality of any central computer record will be carefully guarded and no information by which you can be identified will be released or published. You have been informed that authorized representatives of [INSERT GROUP NAME and the CANCER TRIALS SUPPORT UNIT], the National Cancer Institute, the Food and Drug Administration (FDA), and [INSERT NAME OF INSTITUTION AND INSTITUTIONAL REVIEW BOARD HERE] may inspect and copy the records. *([Optional, if applicable] An authorized representative of the manufacturers of the drugs used in this study may also have access to your study records.)* Your identity will remain confidential and your records will be used by these authorized representatives only in connection with carrying out their obligations relating to the clinical trial and they shall not be used for any other purpose or disclosed to any third party except with your express permission.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds/funds have been set aside to compensate you in the event of injury. (*local institutions must choose the option that best fits the hospital's situation*)

In the case of injury from the venipuncture blood draws for the clonal hematopoiesis testing: Other than medical care that may be provided at the discretion of the treating institution, and any other payment specifically stated in this consent form, there is no other compensation available for your participation in this part of the study. (*paragraph added 12/15/01*)

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

Administration of the drug will be (provided free of charge/charged in the usual way). The parts of the research consisting of keeping research records will be paid by those organizing and conducting the research. The research requires that you receive certain standard medical tests and examinations. These standard tests and examinations will be (charged in the usual way/provided at a reduced rate). (*local institutions must choose the option that best fits the hospital's situation*)

Doxorubicin, cyclophosphamide and trimethoprim sulfa are commercially available. Filgrastim is also commercially available but will be supplied for this study by Amgen Pharmaceutical.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study. We will tell you about important new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the researcher NAME(S) at TELEPHONE NUMBER.

For questions about your rights as a research participant, contact the NAME OF CENTER Institutional Review Board (which is a group of people who review the research to protect your rights) at TELEPHONE NUMBER. [And, if available, list patient representative (or other individual who is not on the research team or IRB).]

WHERE CAN I GET MORE INFORMATION?

[To IRB/Investigators: Attach information materials and checklist of attachments. Signature page should be at the end of package. You may also wish to include the following informational resources]

You may call the NCI's Cancer Information Service at
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

Visit the NCI's Web sites...

cancerTrials: comprehensive clinical trials information <http://cancertrials.nci.nih.gov>.

CancerNet™: accurate cancer information including PDQ
<http://cancernet.nci.nih.gov>.

You will get a copy of this form. You may also request a copy of the protocol (full study plan).

SIGNATURE

You are deciding whether or not to take part in this study. If you sign, it means that you have decided to volunteer to take part in this study, and that you have read and understood all the information on this form.

(changes on signature and lines 12/15/01)

Participant signature _____ Date _____

Participant printed name _____

Consent for submission of samples for clonal hematopoiesis testing: You are agreeing to submit blood samples for the purposes of looking for genetic damage as explained in this form. *(paragraph and lines below added 12/15/01)*

Participant signature _____ Date _____

Participant printed name _____

Witness:

Witness signature _____ Date _____

Witness printed name _____



Southwest Oncology Group Data Operations Center
C/o Cancer Research And Biostatistics
1730 Minor Ave, Suite 1900
Seattle, WA 98101-1468
Patient Registration:
via WebReg at: <http://www.swog.org>

(24 hours a day, 7 days a week, excluding downtimes for maintenance)
or call 206-652-2267 (Mon-Fri, 6:30am-4:00pm Pacific Time, excluding holidays)

Southwest Oncology Group Operations Office
14980 Omicron Drive
San Antonio, TX 78245-3217
Phone: (210) 677-8808
Fax: (210) 677-0006

Southwest Oncology Group Registration Form

SWOG Study No. S 0 0 1 2	Registration Step 1	Assigned Treatment Arm <input type="checkbox"/>	Activation Date: May 1, 2001
Last Amended Date: January 15, 2003			

A Comparative Randomized Study of Standard Doxorubicin and Cyclophosphamide Followed by Weekly Paclitaxel Vs. Weekly Doxorubicin and Daily Oral Cyclophosphamide Plus G-CSF Followed by Weekly Paclitaxel as Neoadjuvant Therapy for Inflammatory and Locally Advanced Breast Cancer

Patient's Name _____

SWOG Patient ID

INSTRUCTIONS: All of the information on this Registration Form and the Protocol Eligibility Section must be answered appropriately for a patient to be considered eligible for registration. This Registration Form must be entirely filled out and referred to during the registration. Do NOT submit this form as part of the patient data.

Caller's SWOG Roster ID

IRB Approval Date

 / /

SWOG Investigator Number

Date Informed Consent Signed

 / /

SWOG Treating Institution Number

Projected Start Date of Treatment

 / /

Patient's Date of Birth: / /

Patient's Sex: Female Male

Method of Payment:

Patient's Ethnicity:

Patient's Race (select all that apply):

White or Caucasian Native Hawaiian or Other Pacific Islander American Indian or Alaska Native
 Black or African American Asian Unknown

If a U.S. resident:

Patient's Social Security Number: - -

Patient's ZIP Code:

Country of Residence, if not USA: _____

If a resident of Canada:

Social Insurance Number: - -

Postal Code: -

Stratification Factors:

Inflammatory disease: No Yes

To which version of the protocol did the patient consent?

Note: Patients registered after January 1, 2003 must consent to Amendment #2 (10/1/2002) version of the protocol.

Version prior to Amendment #2 Amendment #2 (10/1/2002) version

13262

1/15/2003



Southwest Oncology Group Registration Form Code Sheet

Patient's race:

0 - Unknown	1 - Caucasian	2 - African American	3 - Native American
4 - Eskimo	5 - Aleut	6 - Chinese	7 - Filipino
8 - Hawaiian	9 - Korean	10 - Vietnamese	11 - Japanese
12 - Asian Indian	13 - Samoan	14 - Guamanian	15 - Hmong
16 - Fijian	17 - Laotian	18 - Thai	19 - Tongan
20 - Pakistani	21 - Cambodian	22 - Other API	23 - Other race

Patient's Ethnicity (Spanish/Hispanic Origin):

0 - Unknown	1 - No (not Spanish)	2 - Yes, Mexican	3 - Yes, Puerto Rican
4 - Yes, Cuban	5 - Yes, Central American		6 - Yes, South American
7 - Yes, Other	8 - Yes, NOS		

Method of Payment:

1 - Private	2 - Medicare	3 - Medicare and Private	4 - Medicaid
5 - Medicaid and Medicare		7 - No insurance (self-pay)	
8 - No insurance (no means)		9 - Other - specify _____	
10 - Unknown		11 - Veterans Admin	12 - Military

Other Group Registration Code:

9977 - ACOSOG	9981 - NCIC	9982 - CALGB	9984 - GOG
9987 - MDACC	9995 - ECOG	9996 - NCCTG	9997 - RTOG

SOUTHWEST ONCOLOGY GROUP
S0012 BREAST CANCER PRESTUDY FORM

Page 1 of 1

SWOG Patient ID

SWOG Study No. S 0 1 2

Registration Step 1

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Instructions: All dates are MONTH, DAY, YEAR. Explain any blank fields or blank dates in the Comments section at the bottom of the form. Place an **X** in appropriate boxes. Circle AMENDED items in red.

PATIENT CHARACTERISTICS

Menopausal status (select one):

- Pre (< 6 mo since LMP and no prior bilateral ovariectomy and not on estrogen replacement)
 Post (prior bilateral ovariectomy OR > 12 mo since LMP with no prior hysterectomy)
 Above not applicable AND age < 50 (pre) Above not applicable AND age ≥ 50 (post)

Height: cm

Weight: . kg

Performance Status: 0 1 2

DISEASE DESCRIPTION

Date of Initial Diagnosis of Primary Tumor: / /

Stage: IIB IIIA IIIB

Is there a palpable mass or thickening? No Yes If yes, size of mass: . cm

Is there erythema or redness? No Yes If yes, indicate extent: _____

Is there peau d'orange? No Yes If yes, indicate extent: _____

Most Recent Hormone Receptors: (≥ 10 is positive if measured in fmols/mg cytosol protein. Otherwise use institutional standards; borderline results should be reported as positive.)

ER: ER- ER+ Never done or unknown ER

PgR: PgR- PgR+ Never done or unknown PgR

Was HER-2/neu status determined? No Yes

If yes, methods used (select all that apply):

DAKO Herceptest FISH Other IHC, specify: _____

HER-2 Status (select one):

Positive. One or more of the following results were obtained:

- a) 3+ by DAKO Herceptest OR
- b) strongly positive by another immunohistochemical method OR
- c) Her-2 positive as demonstrated by FISH

Negative: otherwise.

PRIOR TREATMENT RELATED TO THIS CANCER

Prior Surgery: Core needle biopsy Incisional biopsy

Date: / /

Comments:



**SOUTHWEST ONCOLOGY GROUP
S0012 AC ASSESSMENT FORM**

Page 1 of 1

SWOG Patient ID

SWOG Study No. S 0 1 2

Registration Step 1

Patient Initials (L, F M)

Date Form Completed: / /

Institution / Affiliate _____

Physician _____

Instructions: Complete after every disease assessment during AC, and submit all completed forms at 6 weeks, 12 weeks, and at time of discontinuation of AC (after final toxicity assessment and before starting paclitaxel). All dates are MONTH, DAY, YEAR.

Explain any blank fields or dates in the **Comments** section. Place an in appropriate boxes. Circle AMENDED data in red.

DISEASE STATUS

Date of Last Disease Assessment:

/ /

Date of Last Contact or Death:

/ /

Vital Status:

Alive
 Dead (submit Notice of Death form)

Is breast normal on physical exam?

No Yes

Is there a palpable mass or thickening?

No Yes

Is there erythema or redness?

No Yes

Is there peau d'orange?

No Yes

Is there a clear increase in disease since registration? No Yes

If Yes, describe increase: _____

New site of disease? No Yes, specify: _____

TREATMENT STATUS

Assigned treatment arm: AC every 3 weeks followed by weekly TAX AC + G-CSF weekly followed by weekly TAX

Is patient still on protocol AC? No (submit Off Treatment Notice) Yes

Were there any dose modifications or additions/omissions to protocol treatment? No Yes

If yes, type and reason: _____

CTC Adverse Event (submit Grades 3 - 5 toxicities since last form only)

Date of Last Toxicity Assessment: / /

Stat Ctr Use Only	GRADE / TERM	Stat Ctr Use Only	GRADE / TERM	Stat Ctr Use Only	GRADE / TERM
CA07	<input type="checkbox"/> Supraventricular arrhythmia	SK13	<input type="checkbox"/> Hand-Foot Syndrome	IN00	<input type="checkbox"/> *Infection w/o 3-4 neutropenia
CA08	<input type="checkbox"/> Ventricular arrhythmia	FL40	<input type="checkbox"/> Fatigue/malaise/lethargy	IN05	<input type="checkbox"/> *Infection with 3-4 neutropenia
CA10	<input type="checkbox"/> LVEF decrease/CHF	HE20	<input type="checkbox"/> Anemia	IN99	<input type="checkbox"/> *Infection, unk ANC
GI00	<input type="checkbox"/> Nausea	HE00	<input type="checkbox"/> Leukopenia	IN30	<input type="checkbox"/> Febrile Neutropenia
GI10	<input type="checkbox"/> Vomiting	HE10	<input type="checkbox"/> Thrombocytopenia	PA99	<input type="checkbox"/> Pain - other
GI20	<input type="checkbox"/> Diarrhea	HE30	<input type="checkbox"/> Neutropenia/ Granulocytopenia		<input type="checkbox"/> Other _____
GI60	<input type="checkbox"/> Stomatitis/pharyngitis	LU00	<input type="checkbox"/> Dyspnea		<input type="checkbox"/> Other _____
GI61	<input type="checkbox"/> Esophagitis/dysphagia				

* Indicate site of infection: _____

Comments:

(TX0012AC)	10/1/2002	23540
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SOUTHWEST ONCOLOGY GROUP
S0012 PACLITAXEL ASSESSMENT FORM

Page 1 of 1

SWOG Patient ID / / / /

SWOG Study No. **S 0 0 1 2**

Registration Step **1**

Patient Initials (L, F M)

Date Form Completed: / /

Institution / Affiliate _____ Physician _____

Instructions: Complete after every disease assessment during paclitaxel treatment, and submit all completed forms at time of discontinuation of paclitaxel (after final toxicity assessment). All dates are MONTH, DAY, YEAR. Explain any blank fields or dates in the **Comments** section. Place an **X** in appropriate boxes. Circle **AMENDED** data in red.

DISEASE STATUS

Date of Last Disease Assessment:

/ / / /

Date of Last Contact or Death:

/ / / /

Vital Status:

- Alive
 Dead (*submit Notice of Death form*)

Is breast normal on physical exam?

No Yes

Is there a palpable mass or thickening?

No Yes

Is there erythema or redness?

No Yes

Is there peau d'orange?

No Yes

Is there a clear increase in disease since registration? No Yes

If Yes, describe increase: _____

New site of disease? No Yes, specify: _____

TREATMENT STATUS

Assigned treatment arm: AC every 3 weeks followed by weekly TAX AC + G-CSF weekly followed by weekly TAX

Is patient still on protocol paclitaxel? No (*submit Off Treatment Notice*) Yes

Were there any dose modifications or additions/omissions to protocol treatment? No Yes

If yes, type and reason: _____

CTC Adverse Event (submit Grades 3 - 5 toxicities since last form only)

Date of Last Toxicity Assessment: / / / /

Stat Ctr Use Only	GRADE / TERM
CA50	<input type="checkbox"/> Hypertension
CA52	<input type="checkbox"/> Thrombosis/embolism
EY42	<input type="checkbox"/> Blurred vision
GI43	<input type="checkbox"/> Taste disturbance
GI63	<input type="checkbox"/> Typhlitis
HE00	<input type="checkbox"/> Leukopenia
HE10	<input type="checkbox"/> Thrombocytopenia
HE20	<input type="checkbox"/> Anemia

Stat Ctr Use Only	GRADE / TERM
HE30	<input type="checkbox"/> Neutropenia/granulocytopenia
IM00	<input type="checkbox"/> Allergy/hypersensitivity
LI00	<input type="checkbox"/> Bilirubin increase
LI11	<input type="checkbox"/> SGOT (AST) increase
LU50	<input type="checkbox"/> Pneumonitis/infiltrates
NR30	<input type="checkbox"/> Seizures
NR51	<input type="checkbox"/> Ataxia

Stat Ctr Use Only	GRADE / TERM
NR60	<input type="checkbox"/> Sensory neuropathy
PA99	<input type="checkbox"/> Pain - other
	Other:
	<input type="checkbox"/>

* Indicate site of infection: _____

Comments:

(TX0012PAC)	10/1/2002	6644
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SOUTHWEST ONCOLOGY GROUP
S0012 DOSE FORM -- ARM 1

Page 1 of 1

SWOG Patient ID

SWOG Study No. S 0 1 2

Registration Step 1

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Instructions: Complete this form if the patient was assigned to **Treatment Arm 1**. Submit this form **only once**, after the patient has completed AC. All dates are MONTH, DAY, YEAR. Explain any blank dates or fields in the **Comments** section. Place an **X** in appropriate boxes. Circle **AMENDED** items in red.

Did the patient start treatment on the assigned arm?

- No (Do not complete the rest of the form.)
 Yes (Do complete the rest of the form.)

DOSE RECEIVED

For each cycle the patient remained on the assigned treatment arm, specify dates of administration and total dose (in mg/m²) received by the patient for each agent. Note: Total dose in mg/m² is calculated by dividing the total dose the patient received in mg by the patient's BSA. Also note: 1 gm = 1,000 mg.

Specify totals for the remaining agent even if the other agent was discontinued early.

<p>BSA (m²): .</p> <p>(measured at baseline)</p>	<p>Cycle 3 Start date: / / </p> <p>CTX total mg/m²: .</p> <p>DOX total mg/m²: .</p> <p>Was G-CSF given? <input type="checkbox"/> No <input type="checkbox"/> Yes</p> <p>If Yes: Total µg/kg per day: .</p> <p>Number of days: </p>
<p>Cycle 1 Start date: / / </p> <p>CTX total mg/m²: .</p> <p>DOX total mg/m²: .</p> <p>Was G-CSF given? <input type="checkbox"/> No <input type="checkbox"/> Yes</p> <p>If Yes: Total µg/kg per day: .</p> <p>Number of days: </p>	<p>Cycle 4 Start date: / / </p> <p>CTX total mg/m²: .</p> <p>DOX total mg/m²: .</p> <p>Was G-CSF given? <input type="checkbox"/> No <input type="checkbox"/> Yes</p> <p>If Yes: Total µg/kg per day: .</p> <p>Number of days: </p>
<p>Cycle 2 Start date: / / </p> <p>CTX total mg/m²: .</p> <p>DOX total mg/m²: .</p> <p>Was G-CSF given? <input type="checkbox"/> No <input type="checkbox"/> Yes</p> <p>If Yes: Total µg/kg per day: .</p> <p>Number of days: </p>	<p>Cycle 5 Start date: / / </p> <p>CTX total mg/m²: .</p> <p>DOX total mg/m²: .</p> <p>Was G-CSF given? <input type="checkbox"/> No <input type="checkbox"/> Yes</p> <p>If Yes: Total µg/kg per day: .</p> <p>Number of days: </p>

Comments:

(TX0012ARM1)

10/1/2002

40274

SOUTHWEST ONCOLOGY GROUP
S0012 DOSE FORM -- ARM 2

Page 1 of 1

SWOG Patient ID

SWOG Study No. S 0 1 2

Registration Step 1

Patient Initials (L, F M)

Institution / Affiliate

Physician

Instructions: Complete this form if the patient was assigned to **Treatment Arm 2**. Submit this form **only once**, after the patient has completed AC. All dates are MONTH, DAY, YEAR. Explain any blank dates or fields in the **Comments** section. Place an **X** in appropriate boxes. Circle **AMENDED** items in red.

Did the patient start treatment on the assigned arm?

- No (Do not complete the rest of the form.)
 Yes (Do complete the rest of the form.)

DOSE RECEIVED

For each week the patient remained on the assigned treatment arm, specify dates of administration and total dose (in mg/m²) received by the patient for each agent. Note: Total dose in mg/m² is calculated by dividing the total dose the patient received in mg by the patient's BSA. Also note: 1 gm = 1,000 mg.

Specify totals for the remaining agent even if the other agent was discontinued early.

BSA (m²): . (measured at baseline)

	Course Begin date	CTX total mg/m ²	DOX total mg/m ²	G-CSF given
Week 1	 / / 	 . 	 . 	<input type="checkbox"/> Yes <input type="checkbox"/> No
Week 2	 / / 	 . 	 . 	<input type="checkbox"/> Yes <input type="checkbox"/> No
Week 3	 / / 	 . 	 . 	<input type="checkbox"/> Yes <input type="checkbox"/> No
Week 4	 / / 	 . 	 . 	<input type="checkbox"/> Yes <input type="checkbox"/> No
Week 5	 / / 	 . 	 . 	<input type="checkbox"/> Yes <input type="checkbox"/> No
Week 6	 / / 	 . 	 . 	<input type="checkbox"/> Yes <input type="checkbox"/> No
Week 7	 / / 	 . 	 . 	<input type="checkbox"/> Yes <input type="checkbox"/> No
Week 8	 / / 	 . 	 . 	<input type="checkbox"/> Yes <input type="checkbox"/> No
Week 9	 / / 	 . 	 . 	<input type="checkbox"/> Yes <input type="checkbox"/> No
Week 10	 / / 	 . 	 . 	<input type="checkbox"/> Yes <input type="checkbox"/> No
Week 11	 / / 	 . 	 . 	<input type="checkbox"/> Yes <input type="checkbox"/> No
Week 12	 / / 	 . 	 . 	<input type="checkbox"/> Yes <input type="checkbox"/> No
Week 13	 / / 	 . 	 . 	<input type="checkbox"/> Yes <input type="checkbox"/> No
Week 14	 / / 	 . 	 . 	<input type="checkbox"/> Yes <input type="checkbox"/> No
Week 15	 / / 	 . 	 . 	<input type="checkbox"/> Yes <input type="checkbox"/> No

Comments:

(TX0012ARM2)

10/1/2002

32573

SOUTHWEST ONCOLOGY GROUP
S0012 PACLITAXEL DOSE FORM - ARM 1 AND ARM 2

Page 1 of 1

SWOG Patient ID

SWOG Study No. S 0 1 2

Registration Step 1

Patient Initials (L, F M)

Institution / Affiliate Physician

Instructions: Submit this form **only once**, after the patient has **completed paclitaxel**. All dates are **MONTH, DAY, YEAR**. Explain any blank dates or fields in the **Comments** section. Place an in appropriate boxes. Circle **AMENDED** items in red.

Assigned treatment arm:

- AC every 3 weeks followed by weekly paclitaxel
- AC + G-CSF weekly followed by weekly paclitaxel

Did the patient start paclitaxel?

- No (Do not complete the rest of the form)
- Yes (Do complete the rest of the form)

PACLITAXEL DOSE RECEIVED

For each week the patient remained on paclitaxel, specify dates of administration and total paclitaxel dose (in mg/m²) received by the patient. Note: Total dose in mg/m² is calculated by dividing the total dose the patient received in mg by the patient's BSA. Also note: 1 gm = 1,000 mg.

BSA (m²): . (measured at baseline)

	Course Begin date	TAX total mg/m ²
Week 1	<input type="text"/> / <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> . <input type="text"/>
Week 2	<input type="text"/> / <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> . <input type="text"/>
Week 3	<input type="text"/> / <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> . <input type="text"/>
Week 4	<input type="text"/> / <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> . <input type="text"/>
Week 5	<input type="text"/> / <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> . <input type="text"/>
Week 6	<input type="text"/> / <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> . <input type="text"/>
Week 7	<input type="text"/> / <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> . <input type="text"/>
Week 8	<input type="text"/> / <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> . <input type="text"/>
Week 9	<input type="text"/> / <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> . <input type="text"/>
Week 10	<input type="text"/> / <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> . <input type="text"/>
Week 11	<input type="text"/> / <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> . <input type="text"/>
Week 12	<input type="text"/> / <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> . <input type="text"/>

Comments:

(TX0012PACDS)

10/1/2002

30365



**SOUTHWEST ONCOLOGY GROUP
OFF TREATMENT NOTICE**

Page 1 of 1

SWOG Patient ID

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SWOG Study No. S

--	--	--	--

Registration Step

--

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Groups other than SWOG: Group Name/Study No./Pt. ID _____ / _____ / _____

Instructions: For each registration step, submit this form within 2 weeks after completion (or discontinuation) of treatment.

Systemic Therapy: List regimens, start and end dates. For multidrug regimens, do not list individual drugs separately; end date would be the date all drugs in the regimen were discontinued.

Surgery: List type of surgery, and in the "end date" column, the date of surgery.

Radiation: List sites, start and end dates (inclusive of boosts and implants).

All dates are MONTH, DAY, YEAR. Explain any blank fields or blank dates in the Notes section. Place an in appropriate boxes. Circle AMENDED items in red.

Treatment Start Date

Treatment End Date

Regimen or Procedure or Site(s)

(If more room is needed, please continue on a separate page)

Off Treatment Reason (select one):

- Treatment completed per protocol criteria
- Medically required, due to toxicity, specify: _____
- Patient refused, due to toxicity, specify: _____
- Patient refused, other than toxicity, specify: _____
- Progression or relapse. Sites: _____
- Death (attach Notice of Death form)
- Other, specify: _____

Off Treatment Date

Date of completion, progression, death or decision to discontinue therapy:

--	--	--	--	--	--	--

Will patient receive further treatment?

No Yes, specify: _____ Unknown

Date of Last Contact (or death):

--	--	--	--	--	--	--

Vital Status: Alive Dead (attach Notice of Death form)

Notes:

--

61571

5/1/2001



**SOUTHWEST ONCOLOGY GROUP
NOTICE OF DEATH**

Page 1 of 1

SWOG Patient ID

--	--	--	--	--

Most Recent SWOG Study No. S

--	--	--	--

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Groups other than SWOG: Group Name/Study No./Pt. ID _____ / _____ / _____

Instructions: Answer all questions and explain any blank fields or blank dates in the Notes section. Place an in appropriate boxes. Circle AMENDED items in red.

Date of Death:

--	--	--	--	--	--

 (month / day / year)

CAUSES OF DEATH

Any cancer (select one):

No Primary Cause Contributory Possible Unknown

If cancer was the primary cause or if cancer possibly or definitely contributed to death, and the patient had had multiple tumor types, specify those which were causes of death:

- Cancer of most recent SWOG study, specify cancer: _____
 Cancer of other SWOG study, specify cancer: _____
 Other cancer, specify: _____

Toxicity from disease related treatment (select one):

No Primary Cause Contributory Possible Unknown

If Primary Cause, Contributory or Possible, specify treatment and toxicity:

Non-cancer and non-treatment related causes (select one):

No Primary Cause Contributory Possible Unknown

If Primary Cause, Contributory or Possible, specify:

Autopsy done? No Yes Unknown

Death information obtained from (select all that apply):

- Autopsy report
 Medical record / Death certificate
 Physician
 Relative or friend
 Other, specify: _____

Notes:

61554

5/1/2001



**SOUTHWEST ONCOLOGY GROUP
FOLLOW UP FORM**

Page 1 of 1

SWOG Patient ID

SWOG Study No. S

Registration Step

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Groups other than SWOG: Group Name/Study No./Pt. ID _____ / _____ / _____

Instructions: Please submit at each follow up after completion of treatment until recurrence, at time of recurrence, and at protocol specified intervals after recurrence. All dates are MONTH, DAY, YEAR. Answer all questions and explain any blank fields or blank dates in the Notes section. Place an in appropriate boxes. Circle AMENDED items in red.

VITAL STATUS

Vital Status: Alive Dead Date of last contact or death: / /

If vital status is Dead, complete and submit Notice of Death form.

DISEASE FOLLOW UP STATUS

Has the patient had a documented clinical assessment for this cancer since submission of the previous follow-up form?

No Yes If Yes, Date of Last Clinical Assessment: / /

NOTICE OF FIRST RELAPSE OR PROGRESSION

Has the patient developed a first relapse or progression that has not been previously reported?

No Yes If Yes, Date of Relapse or Progression: / /

Site(s) of Relapse or Progression: _____

NOTICE OF NEW PRIMARY

Has a new primary cancer or myelodysplastic syndrome (MDS) been diagnosed that has not been previously reported?

No Yes If Yes, Date of Diagnosis: / /

New Primary Site: _____

NON-PROTOCOL TREATMENT

Has the patient received any non-protocol cancer therapy (prior to progression/relapse) not previously reported?

No Yes If Yes, Date of First Non-Protocol Therapy: / /

Agents: _____

LONG TERM TOXICITY

Has the patient experienced (prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment) any severe (grade ≥ 3) long term toxicity that has not been previously reported?

No Yes If Yes, Toxicities and Grades: _____

Notes:

61519

5/1/2001



**SOUTHWEST ONCOLOGY GROUP
SPECIMEN SUBMISSION FORM**

Page 1 of 1

SWOG Patient No.

SWOG Study No.

Reg Type:

Patient Initials _____ (L, F, M) Disease _____

Institution/Member _____ Physician _____

Contact Person at Institution _____ Telephone No. _____

Groups other than SWOG: Group Name/Study No./Pt. No. / / /

Instructions: Submit a SEPARATE Specimen Submission Form with EACH specimen type (e.g.- blood and bone marrow are separate submissions). Check protocol for submission details. All dates are MONTH, DAY, YEAR. Explain any blank fields or dates in the Notes section at the bottom of the form. Place an in appropriate boxes. Circle AMENDED items in red.

SPECIMEN

Type of Specimen: (Check only one)

- Tubes of blood
- Tubes of bone marrow
- Tubes of serum
- Tissue, specify site(s): _____

check one: fresh

frozen

paraffin embedded

Slides, type and number: _____

Karyotype(s), number: _____

Other, specify: _____

Date specimen collected: / /

(month, day, year)

Time specimen collected: :

(24 hour time)

REASONS FOR SPECIMEN SUBMISSION

(Check all that apply)

STATUS

TREATMENT STUDY NO.

Prestudy specimen

Complete remission/response specimen

Relapse/recurrence specimen

Other specimen,

specify: _____

By: _____ Date: _____

Notes from submitting institution:

For Central Laboratory Use Only

Note - Central Laboratory: Complete and return form to SWOG Statistical Center

Central laboratory identification number:

Condition of specimen (check only one):

usable as received

not usable as received; adequate submission

not usable as received; inadequate submission

Date specimen received: / /

Time specimen received: :

By: _____ Date: _____

Notes from central laboratory:

(specsub)

4/1/2000

1951



19.0 APPENDIX

- 19.1 Expanded Participation Project (EPP) Instructions
- 19.2 G-CSF Drug Order Form
- 19.3 Returned Medication Packing Slip
- 19.4 Oral Trimethoprim/Sulfamethoxazole Desensitization Procedure
- 19.5 Clonal Hematopoiesis Assay Descriptions
- 19.6 Post-Surgical Treatment Data Collection Information

19.1 Expanded Participation Project (EPP) Instructions

PROTOCOL: S0012

A Randomized Comparison of Standard Doxorubicin and Cyclophosphamide Vs. Weekly Doxorubicin and Daily Oral Cyclophosphamide Plus G-CSF As Neoadjuvant Therapy For Inflammatory and Estrogen-Receptor Negative Locally Advanced Breast Cancer

1.0 EPP Randomization and Registration Procedures

- I. EPP institutions will register a patient on-line through the Clinical Trials Management Unit (CTMU). Questions pertaining to eligibility criteria should be directed to the CTMU, medical questions should be directed to the Study Chair.
- II. A signed HHS 310 form documenting the Institutional Review Board (IRB) approval for this study must be on file at the CTMU before the EPP institution can enter a patient. IRB approval date must be less than one year prior to the date of registration.
- III. All Investigators must be registered with CTEP, DCTD by the annual submission of the FDA Form 1572 and current CV. To obtain an NCI/CTEP investigator number, investigators should complete and submit (by USMail or Express Courier, faxes are not acceptable) an DFA Form 1572, with an original signature, and current curriculum vitae to the CTMU at:

The EMMES Corporation
401 N. Washington Street
Suite 700
Rockville, MD 20850
Attn: Clinical Trials Management Unit

Upon receipt the CTMU will forward the documents to the Pharmaceutical Management Branch at the NCI for processing. The FDA Form 1572, with instructions, is available on the Forms Section of the EPP web site (www.emmes.com/epp) or by calling the CTMU at 301-251-1161.

- IV. The CTMU will check the investigator and site information provided to ensure that all regulatory requirements have been met. The CTMU protocol monitor will also check the forms for completeness and follow-up with the site to resolve any discrepancies. Once investigator and patient eligibility have been confirmed, the CTMU will contact the SWOG to obtain a randomization assignment. The CTMU will then contact the enrolling site and convey the patient's treatment assignment. This will be followed by a confirmation of registration e-mail or fax to the enrolling site. Please check for errors, and submit any corrections in writing to the CTMU.

2.0 Data Submission

Data must be submitted electronically directly to the CTMU according to the following schedule:

FORM	TIME OF SUBMISSION
S0012 Eligibility Checklist	At registration
S0012 Breast Cancer On-Study Form*	Within 2 weeks of registration
EPP Toxicity Form	Months 1, 2, 3, and every three months while on protocol therapy
EPP Follow-up Form**	Every 3 months while on protocol treatment and every year after completion of protocol treatment until 4 years after randomization
EPP Response/Progression Form**	Every 3 months while on protocol treatment, every 6 months thereafter until progression/relapse
EPP Solid Tumor Evaluation Forms - Target Lesions ⁺	Every 3 months until progression
EPP Solid Tumor Evaluation Forms - Non-Target Lesions ⁺	Every 3 months until progression
EPP Chemotherapy/Immunotherapy/Hormonal Therapy Form*	Initial dose and date agent first administered within 2 weeks of start of therapy. Remainder of form at the completion of protocol therapy.
EPP Off-Treatment Form*	At the completion of all protocol therapy
EPP Notice of Secondary Malignancy Form*	Within 10 days of diagnosis
NCI/CTEP Secondary AML/MDS Report Form	Within 30 days of diagnosis of AML or MDS
EPP Death Form*	Within 7 days of knowledge of event

* These forms are to be submitted according to the above schedule for all patients who never started treatment.

+ If a patient is still alive after 4 years have elapsed after registration, no further follow-up is required.

3.0 EPP Adverse Event (AE) Reporting

A hyperlink to the CTEP home page that contains CTC version 2.0 for toxicity and adverse event reporting is available on the EPP web-site. EPP investigators are responsible for reporting adverse events according to the guidelines provided below, including notification to their local IRB. All reporting should be conducted within the time frames below, and completed forms should be submitted to the CTMU as outlined below. Once received, the CTMU will forward the forms to the SWOG, who will forward them to the appropriate authorities.

3.1 Explanation of terms used in adverse event reporting

Adverse event (AE) - An adverse event is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure.

To select the correct toxicity name for an adverse event, refer to the NCI's Common Toxicity Criteria (CTC) Version 2.0. The NCI has an available Index to the CTC Version 2.0 that provides help for classifying and locating toxicities. The CTC can be found on the Cancer Therapy Evaluation Program (CTEP) homepage at <http://ctep.info.nih.gov/CTC3/ctc.html>. If you need further assistance, please contact the CTMU.

Grade - The NCI Common Toxicity Criteria (CTC) Version 2.0 must be used to determine the grade (severity) of the adverse event.

Attribution - Attribution is defined as the determination of whether an adverse event is related to a medical treatment or procedure. Attribution categories are as follows:

- Unrelated The adverse event is clearly NOT related to the commercial agent (s).
- Unlikely to be related The adverse event is doubtfully related to the commercial agent (s).
- Possibly related The adverse event may be related to the commercial agent (s).
- Probably related The adverse event is likely related to the commercial agent (s).
- Definitely related The adverse event is clearly related to the commercial agent (s).

Expectedness - an adverse event is *unexpected* (unknown) if the type of event (or its specificity or severity) is not listed in the drug package insert or the Physician's Desk Reference (PDR). It is *expected* (known) if it has been reported previously by other physicians and is listed in the drug package insert or the PDR.

Commercial Agent - a commercial agent is any drug included in the protocol therapy that is not supplied under an Investigational New Drug Application (IND). In S0012, the commercial agents are Cyclophosphamide (Cytoxan), Doxorubicin and Filgrastim (G-CSF).

Investigational Agent - an investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In S0012, there are no investigational agents.

Treatment that contains both investigational and commercial agents should be reported according to the investigational guidelines. However, if the reaction is clearly a known reaction of the commercial agent involved, it should be reported according to the commercial agent guidelines.

3.2 Procedures for reporting

Adverse event monitoring and reporting is a routine part of every clinical trial. Grade the severity of the event using the CTC v. 2.0. Then, determine whether the event is expected or unexpected (refer to Section 3.0 of the protocol, Drug Information) and if the adverse event is related to the medical treatment or procedure. With this information, determine whether an adverse event should be reported as an expedited report or as part of the routinely reported clinical data. All grades of all adverse events felt to be at least possibly treatment related, including those with separate reporting requirements described in the Table below, should be reported on the EPP Toxicity Form.

Expedited adverse event reporting requires submission of a written report to the CTMU. Telephone notification of NCI and CTMU may also be required. Telephone and written reports are to be completed within the timeframes specified in the table below. All expedited adverse event reports should also be submitted to the local Institutional Review Board (IRB).

Deaths are required to be reported via the EPP Death Form within 7 days of knowledge of the event. Any death more than 30 days after the patient's last study treatment or procedure which is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTC type and attribution assigned.

**3.3 Expedited Adverse Event Reporting Requirements (based on NCI Guidelines:
Expedited Reporting Requirements for NCI Commercial Agents, January 2001
Version)**

	Grade 4 or 5 Unexpected Regardless of Attribution	Grade 5 Expected with Attribution of Possible, Probable or Definite	Secondary AML/MDS¹
Written report to CTMU within 5 working days ^{2,3,4}	X	X	
NCI/CTEP Secondary AML/MDS Report Form to CTMU within 10 working days ³			X

1. Reporting for this AE required during or after treatment.
2. Use *Form FDA-3500* available on the EPP website.
3. Fax or mail reports to the CTMU, The EMMES Corporation, 11325 Seven Locks Road Suite 214, Potomac, MD 20854, Fax: 301-299-3991. The CTMU will submit the report to the SWOG and NCI, as required.
4. Grade 4 myelosuppression are not submitted via this form.

If a patient has been on more than one NCI-sponsored study, the NCI/CTEP Secondary AML/MDS Report form must be submitted for the most recent trial.

Remove patient names and identifiers such as social security number, address, etc., from reports and supporting documentation that may be forwarded to the IDB.

3.4 Pregnancy occurring while the patient is on protocol therapy

If a patient of an EPP investigator becomes pregnant while receiving protocol therapy, the CTMU Protocol Monitor (epppm@emmes.com) should be notified immediately.

This page was deleted.

Study Title: S0012, A Comparative Randomized Study of Standard Doxorubicin And Cyclophosphamide Vs. Weekly Doxorubicin And Daily Oral Cyclophosphamide Plus G-CSF As Neoadjuvant Therapy For Inflammatory And Estrogen Receptor Negative Locally Advanced Breast Cancer

Filgrastim (G-CSF) Drug Request Form

Requested by:

Ship To:

Pharmacist:

Name:

Institution:

Address*:

Principal Investigator:

* Please do not use P.O. Box numbers

Phone #:

Fax:

**** Reminder: See protocol section on drug formulation for instructions regarding amounts of drug to order.**

G-CSF will be shipped (refrigerated) on Monday through Thursday for next day delivery.

Orders received by 11:30 am pacific time Monday through Thursday will be shipped the same day.

Date of Drug Request

Pharmacist Signature

Return Completed, Signed, and Dated form to:

UintaVision, Inc./Axion, Inc.
Fax: 650-745-3877

RETURNED MEDICATION PACKING SLIP

Institution Name:

Address:

Principal Investigator:

Phone No.:

Amgen Study No:

Cooperative Group No.: S0012

Study Title: "A Comparative Randomized Study of Standard Doxorubicin And Cyclophosphamide Vs. Weekly Doxorubicin And Daily Oral Cyclophosphamide Plus G-CSF As Neoadjuvant Therapy For Inflammatory And Estrogen-Receptor Negative Locally Advanced Breast Cancer"

Instructions:

Per FDA requirements, please retain a copy of this completed form for your files. Drug being returned for any reason should be sent, together with this original form, to Oncology Therapeutics Network OTN), 395 Oyster Point Boulevard, Suite 405, South San Francisco, CA 94080. Questions may be directed to (800) 370-2508, Monday through Friday 8:00 am - 5:00 pm, Pacific Standard Time. Voice Mail is available at all other times.

Study in progress?

Person Shipping Drug:

Yes No

Drug being returned by:

Study completed per protocol?

Fed Ex UPS US Mail

Yes No

Date: No. of cartons:

Reason drug returned? (Please check one)

Data Manager's/Pharmacist's Signature:

Drug Expired

Date:

Unused drug being returned

Return receipt requested: Yes No

DESCRIPTION OF RETURN SHIPMENT

TO BE COMPLETED BY AMGEN

Returned shipment received on _____ and checked by: _____
(Date) (Name)

19.4 ORAL TRIMETHOPRIM/SULFAMETHOXAZOLE DESENSITIZATION PROCEDURE

This is completed over six days with oral doses of TMP/SMX (trimethoprim/sulfamethoxazole, or "Bactrim"). One standard double-strength (DS) Bactrim tablet contains 160 mg of TMP and 800 mg of SMX. Desensitization is performed with solutions made from a standard oral suspension of TMP/SMX, which consists of 40 mg TMP and 200 mg SMX per 5 ml. The dilutions and final concentrations for TMP and SMX components are given below.

<u>Day 1</u>	1:100,000 dilution	(0.0004 mg SMX in 1 cc) (0.00008 mg TMP in 1 cc)
1 cc*		
2 cc*	QID	
4 cc		
8 cc		

- * The first two doses should be administered in the clinic and patients should be observed for anaphylaxis for one hour after each of these two doses, with appropriate medications and equipment available for resuscitation. **Someone must be present who can observe and summon help if anaphylaxis occurs.**

<u>Day 2</u>	1:10,000 dilution	(0.004 mg SMX in 1 cc) (0.0008 mg TMP in 1 cc)
1 cc		
2 cc	QID	
4 cc		
8 cc		

<u>Day 3</u>	1:1,000 dilution	(0.04 mg SMX in 1 cc) (0.008 mg TMP in 1 cc)
1 cc		
2 cc	QID	
4 cc		
8 cc		

<u>Day 4</u>	1:100 dilution	(0.4 mg SMX in 1 cc) (0.08 mg TMP in 1 cc)
1 cc		
2 cc	QID	
4 cc		
8 cc		

<u>Day 5</u>	1:10 dilution	(4.0 mg SMX in 1 cc) (0.8 mg TMP in 1 cc)
1 cc		
2 cc	QID	
4 cc		
8 cc		

Day 6 Standard oral susp. (40.0 mg SMX in 1 cc)
(8.0 mg TMP in 1 cc)

1 cc
2 cc
4 cc
8 cc

Following Day 6, take one DS (double strength, 800 mg) tablet Bactrim every day until chemotherapy is complete. **IT IS IMPORTANT TO NOT MISS A DAY.**

If symptoms develop, the following interventions are recommended:

<u>SYMPTOM</u>	<u>TREATMENT</u>
Low grade fever, malaise, myalgia	Aspirin, Tylenol q 4 hrs as needed
Mild morbilliform eruption	Diphenhydramine hydrochloride 25-50 mg q 6-8 h prn; 50 mg hs
Raging fever and/or florid morbilliform rash: urgent care	Prednisone 60 mg daily for 3 days, then 40 mg daily for 3 days, then 20 mg daily for 3 days, then 10 mg daily for 3 days
Shortness of breath	Call 911

NOTE: Patients failing desensitization or intolerant to sulfa may receive pentamidine at the treating physician's discretion.

19.5 Clonal Hematopoiesis Assay Descriptions

Sample Processing:

High molecular weight DNA will be prepared from the blood and apheresis samples following Ficoll-gradient separation, according to standard proteinase K digestion and phenol/chloroform extraction methods. (53) Cells from each blood samples (a minimum of 20 - 30 x10⁶ cells) will be frozen for variability according to standard methods. (54)

HUMARA assay: DNA samples from each of the 200 patients enrolled will be studied at the time points outlined previously. Clonality at the HUMARA locus will be assessed by PCR amplification according to Willman et al. using the primers described by Gale et al., and quantitated by the method of Delabesse et al. (48, 55, 56) Willman et al have performed mixing experiments which demonstrate that the percentage of clonal cells can be estimated with an error of ± 10%, and that a clonal population of cells can be detected if they constitute more than 10 percent of the cells in a polyclonal background. (48) Assays will performed in duplicate or triplicate.

Microsatellite instability assay: Microsatellite instability will be assessed at multiple chromosomal loci: 7q31 (D7S522 marker), 5q31 (Mfd27 marker), 17p12 (Mfd41 marker), 8p22 (LPL marker), 11q23(D11S939 marker) and the BAT loci (25, 26 and 40). (57-63) Although the microsatellite assay is a general assay for genomic instability, we have chosen highly polymorphic microsatellites from regions known to be associated with t-MDS/AML since these markers may also provide information about loss of heterozygosity in these genomic regions. The PCR assays will be done in duplicate according to published methods. (52)

Detection of MLL gene rearrangements and RAS mutations: In cases where the HUMARA or microsatellite repeat assays are positive for clonal hematopoiesis, sensitive reverse-transcriptase PCR assays, using RNA from banked specimens, will be used to detect MLL fusion transcripts commonly reported in AML with 11q23 abnormalities. (64, 65) RAS mutations will be performed according to published methods. (31, 42)

19.6 Post-Surgical Treatment Data Collection.

All post-surgical treatment must be documented on the Southwest Oncology Group Follow-Up Form (Form #61519). This information may be included in the "Notes" section of the form. If more space is needed, an additional sheet may be attached to the Follow-Up Form and the additional sheet must include the study number, patient's initials and patient number.

Record each chemotherapy agent given and include doses and dates, if available. Record any radiation therapy with a description of the sites irradiated, dates and doses, if available.